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One-pot pseudo three-component reaction of nitroketene-*N*,*S*-acetals and aldehydes for synthesis of highly functionalized hexa-substituted 1,4-dihydropyridines†

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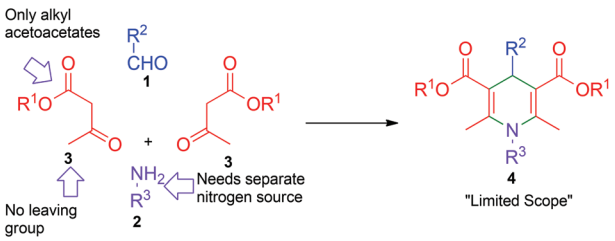
We have described the simple, convenient and high yielding one-pot synthesis of a library of highly functionalized hexa-substituted 1,4-dihydropyridines (1,4-DHPs) by 2-aminopyridine catalysed pseudo three-component reaction of nitroketene-*N*,*S*-acetals and aldehydes. This domino transformation involves formation of dihydropyridine ring by creation of two C–C bonds and one C–N bond, all of them taking place in a single synthetic operation. As the products precipitate out of the reaction simple filtration is enough to gather the products and thus, there is no need for work-up or column-chromatography. The C6-methylsulfanyl group in the product 1,4-DHPs was substituted with primary and secondary amines to provide 1,4-DHPs with further possibilities in structural diversity. As a demonstration of application of the method we have synthesised an analogue of nitenpyram, a neonicotinoid insecticide.

Introduction

The multicomponent reactions (MCRs) are among the simplest, atom-economic and eco-friendly reactions used for synthesis of complex molecules from readily available bench-top organic chemicals.[1] On their way to generation of complex products, MCRs go through cascade reactions resulting in formation of several bonds within a single pot. Owing to such highly desirable reaction features that include chemo- and regioselective formation of the products in high yield and purity, in recent years, MCRs have garnered a great deal of attention for synthesis of structurally diverse and densely functionalized biologically and medicinally important products.[2] Classical Hantzsch 1,4-dihydropyridine (1,4-DHP) synthesis in which one unit each of an aldehyde **1**, an amine **2** and two units of acetoacetic ester **3**, undergo four-component MCRs to provide 1,4-DHPs **4** is a quintessential reaction for synthesis of a large library of six-member nitrogen heterocycles (Scheme 1).[3] The 1,4-DHPs are of immense biological importance, as they are analogues of the reactive portion of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH), both of which are cofactors in the enzymes that perform oxidation–reduction reactions.[4] Synthetic 1,4-DHPs found extensive medicinal applications[5] including use as calcium channel blockers,[6] antitumor agents,[7] and anti-inflammatory molecules.[8] Due to the highly specific activity of 1,4-DHPs as calcium channel blocking agents and ease in bulk-scale synthesis, their derivatives, for example nifedipine, became standard drugs for treatment of coronary heart diseases.[9] In addition to medicinal applications, some 1,4-DHPs, like neonicotinoids, exhibit insecticidal activity without being very toxic to humans.[10] Apart from the above applications 1,4-DHPs are used as a hydride source in reduction reactions[11] and as synthetic intermediates in alkaloid syntheses.[12] Owing to diverse applications, 1,4-DHP has become a privileged scaffold and the group has attracted considerable attention for the preparation of structurally diverse six-member nitrogen heterocycles and equally for methodology development.[13] Although, Hantzsch 1,4-DHP synthesis is



Scheme 1 Hantzsch 1,4-dihydropyridine synthesis and limitations.

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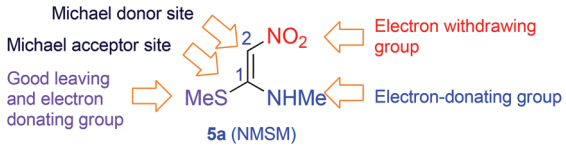


Fig. 1 Structure and reactivity profile of NMSM **5a**.

hugely popular, it has some limitations like being restricted to alkyl acetoacetates, the need for a separate nitrogen source, difficulty in further functionalization of the alkyl group, *etc.* (Scheme 1). Hence, development of new methods by overcoming such difficulties for diversity oriented synthesis of polysubstituted 1,4-DHPs is of great interest.

In continuation of our efforts in exploring the chemistry of nitroketene-*N*,*S*-acetals,[14] we conceived a simple and convenient synthesis of highly functionalized 1,4-DHPs by pseudo MCR of aldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (*N*-*m*ethyl-*S*-*m*ethyl nitroethylene, NMSM) **5a** (Fig. 1) and their analogues. For their simplicity and reactivity pattern (Fig. 1) nitroenamines like NMSM are attractive substrates for synthesis of a variety of heterocyclic compounds.[15] Recently, Tobe and co-workers reported the synthesis of C4-substituted 3,5-dinitro-1,4-DHPs, molecules relevant to the present study, by pseudo three-component condensation involving two equivalents of 2-formyl-2-nitroenamine (specifically 2-nitro-3-(propylamino)acrylaldehyde) and one equivalent electron-rich aromatic compound.[16] By taking the reactivity pattern of NMSM **5a** as enumerated in Fig. 1 into consideration, we performed a Hantzsch type pseudo four-component condensation of two mole equivalents of NMSM **5a** with one mole equivalent each of benzaldehyde **1a** and benzylamine **2a** in refluxing ethanol with the intention to generate 1,4-DHP **6** (Scheme 2). The reaction, surprisingly however, provided its regioisomer 1,4-DHP **7a** exclusively. In the formation of **7a** benzylamine appeared to replace the methylsulfanyl group located on the initially formed 1,4-DHP **8a**. When the reaction of NMSM **5a** and benzaldehyde **1a** was conducted in the presence of a catalytic amount of benzylamine **2a** (10 mol%) the 1,4-DHP **8a** was the major product (71%) and **7a** was the minor product (9%). We explored the reaction further and present here its scope for the synthesis of a library of 1,4-DHPs **7** and **8** and for the facile synthesis of an analogue of neonicotinoid insecticide.

Results and discussion

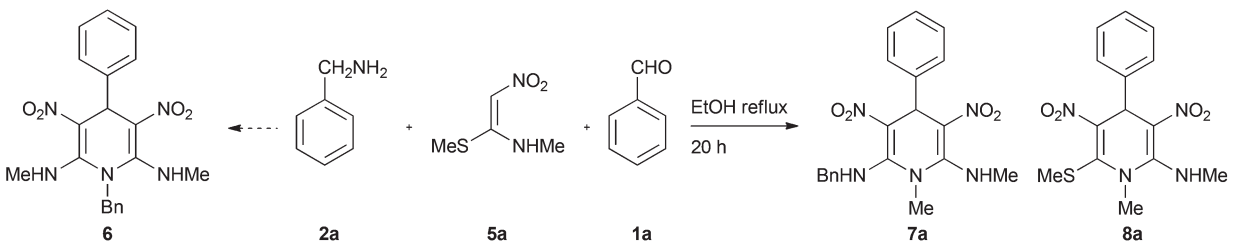
Our initial studies were focused on identification of optimal reaction conditions for the pseudo MCR of benzaldehyde **1a** and NMSM **5a** to afford 1,4-DHP **8a** (Table 1). The reaction did not take place in the absence of a base catalyst (Table 1, entry 1). A series of the reactions was then performed with a catalytic amount (10 mol%) of base which included non-nucleophilic tertiary amines like 4-(dimethylamino)pyridine

Table 1 Optimization of reaction conditions for pseudo MCRs leading to **8a**

1a **5a** **8a**

Entry	Base[a] (equivalents)	Solvent	Time (h)	Yield (%)
1	No catalyst	EtOH	24	—
2	DMAP (0.1)	EtOH	15	30
3	DBU (0.1)	EtOH	20	10
4	Et_3N (0.1)	EtOH	20	26
5	Pyridine (0.1)	EtOH	10	20
6	Piperidine (0.1)	EtOH	15	38
7	Pyrrolidine (0.1)	EtOH	10	36
8	L-Proline (0.1)	EtOH	15	46
9	Benzylamine (0.1)	EtOH	20	71
10	Ethyl amine (0.1)	EtOH	12	62
11	Aniline (0.1)	EtOH	15	62
12	**2-AP (0.1)**	**EtOH**	**5**	**92**
13	4-AP (0.1)	EtOH	10	71
14	K_2CO_3 (0.1)	EtOH	15	23
15	2-AP (0.05)	EtOH	20	70
16	2-AP (0.01)	EtOH	15	62
17	2-AP (0.001)	EtOH	25	60
18	2-AP (1)	EtOH	2	92
19	2-AP (0.1)	H_2O	20	40
20	2-AP (0.1)	EtOH–H_2O	15	75
21	2-AP (0.1)	MeOH	10	85
22	2-AP (0.1)	DMF	15	62
23	2-AP (0.1)	Toluene	24	65

[a] DMAP: 4-(dimethylamino)pyridine; DBU: 1,8-diazabicycloundec-7-ene; AP: aminopyridine; DMF: *N*,*N*-dimethylformamide.



6 **2a** **5a** **1a** **7a** **8a**

Scheme 2 The pseudo four-component reaction of aldehyde **1a**, NMSM **5a** and benzylamine **2a** for the synthesis of 1,4-DHP **7a**.

(DMAP; entry 2), 1,8-diazabicycloundec-7-ene (DBU; entry 3), triethylamine (entry 4) and pyridine (entry 5) in EtOH medium. In each case 1,4-DHP **8a** was obtained in poor yield. Although the yield of the desired product **8a** improved when secondary amines like piperidine (entry 6), pyrrolidine (entry 7) and L-proline (entry 8) were employed, still the yield was only moderate and much lower than when primary amine bases like benzyl amine (entry 9), 30% aq. solution of ethyl amine (entry 10) or aniline (entry 11) were employed. The real breakthrough appeared when we employed 10 mol% of 2-aminopyridine (2-AP; entry 12) and the reaction provided over 92% yield consistently. The yield of **8a** was lower when 4-aminopyridine (entry 13) or inorganic bases, *e.g.* potassium carbonate (entry 14), were employed. Next, we varied the amount of the 2-AP to evaluate the minimum amount required to furnish **8a** in near quantitative yield. The set of experiments (entries 15–17) showed that 10 mol% of 2-AP provides products in high purity in over 92% yield.

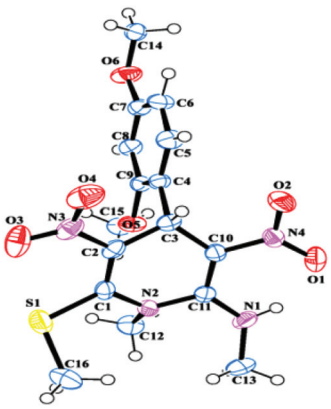
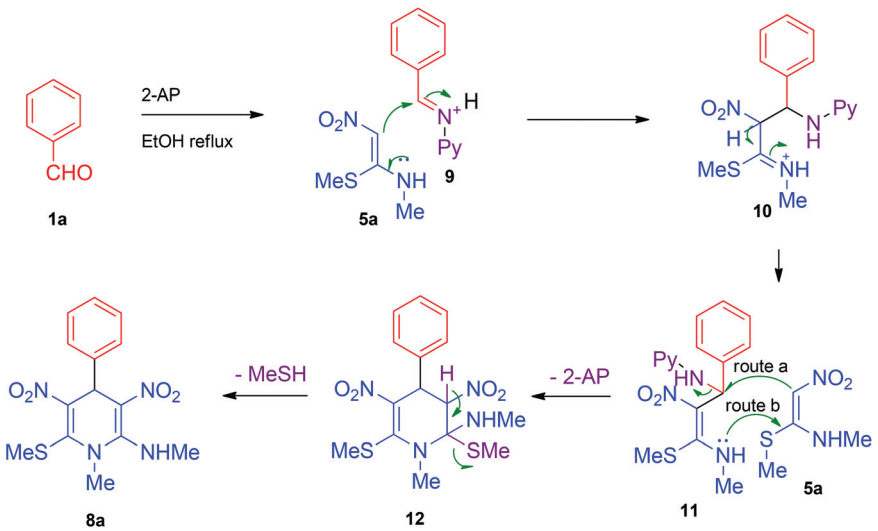


Fig. 2 ORTEP diagram of the 4-(2,4-dimethoxyphenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8i**.

With 1 equivalent of 2-AP the product **8a** was formed in over 92% yield within 2 h (entry 18), but the product required chromatographic purification. Although the reaction proceeded in various solvents like water (entry 19), 1 : 1 mixture of water and ethanol (entry 20), methanol (entry 21), dimethylformamide (entry 22) and toluene (entry 23) at respective solvent reflux temperature, refluxing ethanol was selected for optimized reaction conditions. Under these conditions, yellow colored product **8a** precipitated from the reaction mixture and simple filtration was enough to collect the spectroscopic grade product.

The 1,4-DHP **8a** was characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR spectral data and HRMS analysis. The ^{1}H NMR spectrum of **8a** displayed a characteristic signal for C4*H* at 5.94 ppm. The signals located at δ 2.53, 3.09 and 3.42 attributable to SMe, NHMe and NMe, respectively, supported the assigned structure. The ^{13}C NMR spectrum of **8a** displayed the anticipated 12 signals out of which four were located in the aliphatic region. The structure of **8i** was unequivocally assigned on the basis of single crystal X-ray structure analysis (Fig. 2).

Based on the above results, a plausible mechanism was proposed as shown in Scheme 3. In the first step benzaldehyde **1a** reacts with 2-AP to form the iminium ion **9**. The iminium ion then reacts with NMSM **5a** to generate intermediate **10** which quickly rearranges to the more stable intermediate **11** where the nitroketene-*N*,*S*-acetal substructure has been restored. The intermediate **11** reacts with one more unit of NMSM **5a** to generate intermediate **12** and 2-AP. Finally, an intramolecular elimination of methanethiol furnishes 1,4-DHP **8a**. Formation of iminium ion **9** as the initial intermediate is indicated by the fact that primary amines efficiently promote the pseudo MCR (Table 1). Nucleophilic base 2-AP appears to have the unique ability to form an imine by reacting with benzaldehyde **1a** but not displace the methylsulfanyl group in **8a**. The reaction of intermediate **11** with a second unit of NMSM **5a** could go



Scheme 3 Plausible mechanism for the formation of 1,4-DHP **8a**.

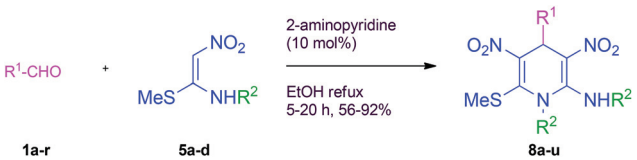
through several pathways, like formation of C–C bond (route a, Scheme 3) ahead of C–N bond formation (route b, Scheme 3) or the other way. Although confirmative evidences are not available at present, we presume that route a is more feasible than b (Scheme 3) as nucleophilic primary amines like benzyl amine did not react with NMSM to provide **6** or **7a** as the primary product (Scheme 2). The reaction of intermediate **11** with **5a** could go through an aza-Diels–Alder pathway. However, taking into consideration the low reactivity of NMSM **5a** towards Diels–Alder reactions[17] we assume this pathway is unlikely.

The 1,4-DHPs **8** have two potential areas for development of structural diversity, namely the aldehyde and the *N*-alkyl groups, which can be exploited for preparation of a library of two-dimensional matrix. We employed the optimized reaction conditions for construction of a small library of 1,4-DHPs **8a–u** (Table 2, Fig. 3). Initially, variations were incorporated in the benzaldehyde ring by placing electron-withdrawing or electron-donating groups in the C4 position (Table 2, entries 2–8) and the products **8b–h** were obtained in good yields. The results indicated that the electron-donating or withdrawing groups had little influence on the outcome of the reaction. Introduction of steric effects at the C2-position of benzaldehyde (entries 9–10) in the form of OMe group did not have any effect on the formation of 1,4-DHPs **8i–j**. Similarly, naphthaldehyde (entry 11) provided the 1,4-DHP **8k** without much difficulty. This methodology was tested with cinnamaldehyde (entry 12) for the formation of 1,4-DHP **8l** and the results indicated that the α,β-unsaturation does not have much influence. An aliphatic aldehyde, *e.g.* hexanal (entry 13), furnished 1,4-DHP **8m** in good yield. The pseudo MCR was next performed with various heterocyclic aromatic aldehydes like thiophene-2-carbaldehyde **1n**, furan-2-carbaldehyde **1o**, 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1p**, pyridine-3-carbaldehyde **1q** and indole-3-carbaldehyde **1r** (entries 14–18) to result in the corresponding 1,4-DHPs **8n–r** in good yield.

After demonstrating the ease of synthesis of 1,4-DHPs **8b–r** by incorporating various changes in the aldehyde portion, we have taken up the synthesis of 1,4-DHPs where diversity is built into *N*-alkyl group. The reaction of nitroketene-*N*,*S*-acetals with *N*-benzyl **5b**, *N*-4-methoxyphenylethyl **5c** and *n*-butyl **5d** groups afforded the corresponding 1,4-DHPs **8s–u** (entries 19–21) without much difficulty. However, the reaction with the nitroketene-*N*,*S*-acetal with *N*-phenyl group did not furnish the desired 1,4-DHP, possibly due to steric repulsion that gets inbuilt when the product is formed. Spectroscopic data of 1,4-dihydropyridines **8b–u** compared well with those of the parent compound **8a**.

The 1,4-dihydropyridines **8** possess a highly labile SMe group, which can be replaced with a variety of nucleophiles by S_NV substitution.[18] For the present study, we have selected to replace the C6 methylsulfanyl group in **8a** with a variety of aliphatic primary and secondary amines. Thus, the reaction of 1,4-DHP **8a** with 1 equivalent of primary amines like benzyl amine **2a**, phenylethyl amine **2b**, *n*-butyl amine **2c**, and *n*-hexyl

Table 2 Synthesis of hexa-substituted 1,4-dihydropyridines (**8a–8u**)[a]



1a-r 5a-d 8a-u

Entry	R^1 in **1**	R^2 in **5**	1,4-DHP **8**	Time (h)	Yield[b] (%)
1	Ph	Me	**8a**	5	92
2	*p*-FC_6H_4	Me	**8b**	6	89
3	*p*-ClC_6H_4	Me	**8c**	12	60
4	*p*-BrC_6H_4	Me	**8d**	12	86
5	*o*-$O_2NC_6H_4$	Me	**8e**	20	56
6	*p*-MeC_6H_4	Me	**8f**	10	75
7	*p*-$MeOC_6H_4$	Me	**8g**	6	85
8	*p*-HOC_6H_4	Me	**8h**	15	62
9	*o*,*p*-$(MeO)_2C_6H_3$	Me	**8i**	5	88
10	*p*-HO,*o*-$MeOC_6H_3$	Me	**8j**	15	82
11	Naphthalene-2-yl	Me	**8k**	6	90
12	Styryl	Me	**8l**	18	73
13	Pentyl	Me	**8m**	20	64
14	Thiophen-2-yl	Me	**8n**	10	70
15	Furan-2-yl	Me	**8o**	15	90
16	1,3-Biphenyl-1*H*-pyrazol-4-yl	Me	**8p**	12	78
17	Pyridine-3-yl	Me	**8q**	15	76
18	Indol-3-yl	Me	**8r**	15	69
19	Ph	Bn	**8s**	20	84
20	Ph	4-$MeOC_6H_4CH_2CH_2$	**8t**	10	86
21	Ph	*n*-Butyl	**8u**	15	70

[a] General conditions: **1** (1 equivalent), **5** (2 equivalents) and 2-aminopyridine (0.1 equivalent) in refluxing ethanol. [b] Isolated yield after triturating with cold (0–5 °C) ethanol.

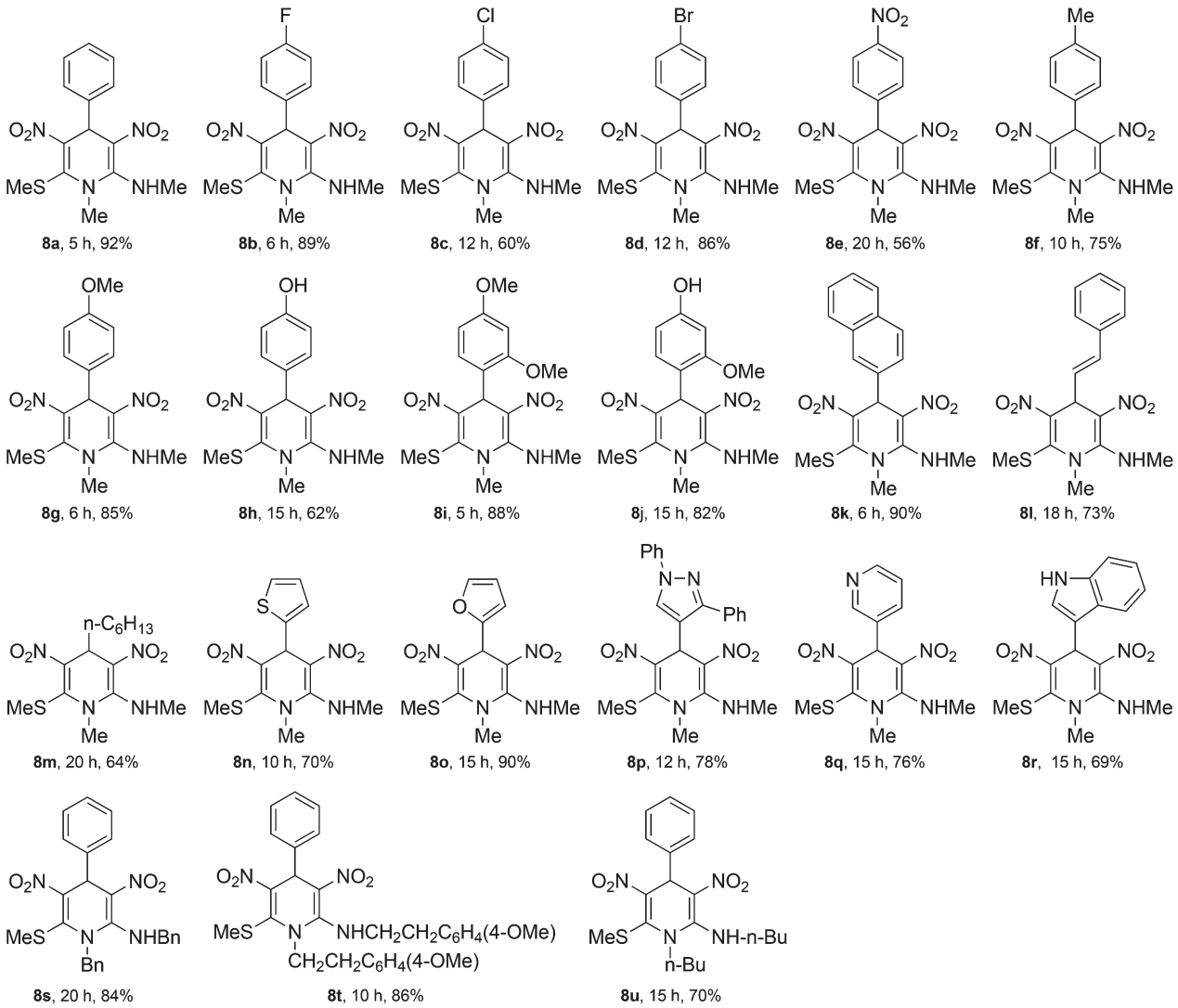
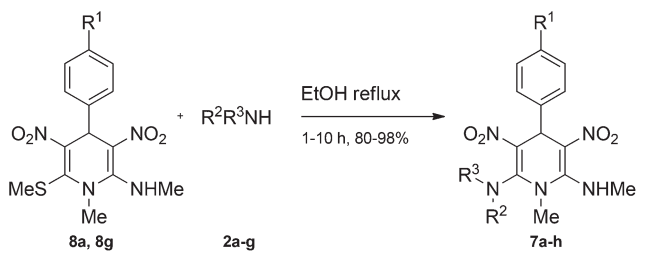


Fig. 3 Library of diversity incorporated 1,4-DHPs with C6-methylthio group.

amine **2d** in refluxing EtOH afforded the corresponding 1,4-DHPs **7a–d** in good yields (Scheme 4, Table 3, entries 1–4). The above experiments showed that it is possible to synthesise a library of 1,4-DHPs that possess three areas of structural diversity, derived from the aldehydes **1**, amine in *N*,*S*-acetals **5** and amines **2** (Scheme 4). To demonstrate this premise on one example, the 1,4-DHP **8g** where the C4-aryl ring is derived from 4-methoxybenzaldehyde was subjected to reaction with benzylamine and the product **7e** was isolated without any difficulty (Table 3, entry 5). Although the reaction took longer, the methylsulfanyl group in 1,4-DHP **8a**, could be replaced with secondary amines like *N*,*N*-dimethylamine **2e**, *N*,*N*-diethylamine **2f** and morpholine **2g** afforded the corresponding



Scheme 4 Synthesis of 1,4-dihydropyridines (**7a–h**) by nucleophilic displacement of the C6 methylsulfanyl group in **8a** with primary or secondary amines and **8g** with benzylamine.

Table 3 Replacement of SMe in **8a** and **8g** by primary and secondary amines

Entry	R^1	R^2 in **2**	R^3 in **2**	Product	Time (h)	Yield (%)
1	H	Bn	H	**7a**	1	98
2	H	Phenylethyl	H	**7b**	1	90
3	H	*n*-Bu	H	**7c**	2	81
4	H	*n*-Hexyl	H	**7d**	5	80
5	OMe	Bn	H	**7e**	2	96
6	H	Me	Me	**7f**	5	92
7	H	Et	Et	**7g**	6	82
8	H	Morpholine	H	**7h**	10	81

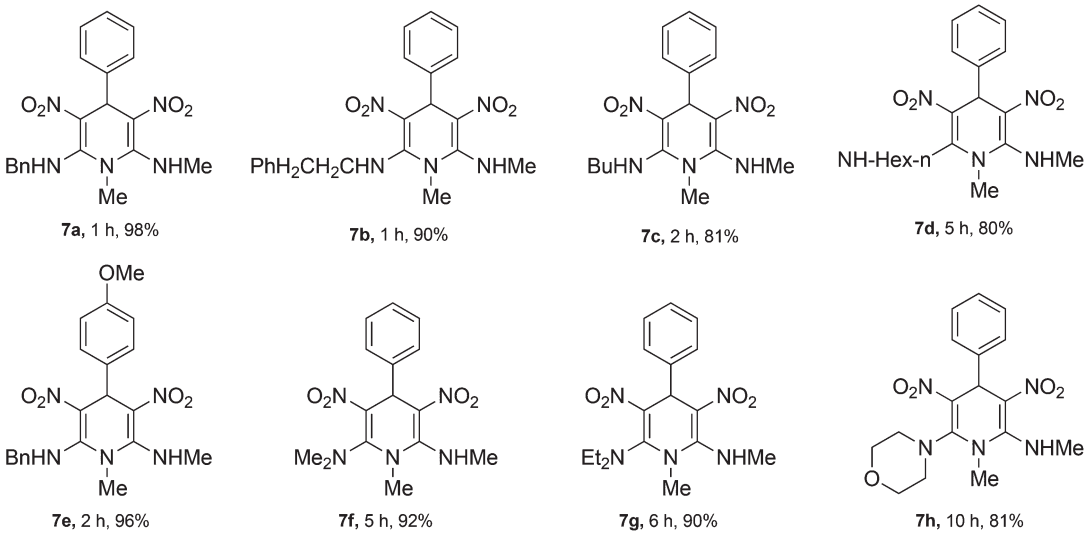
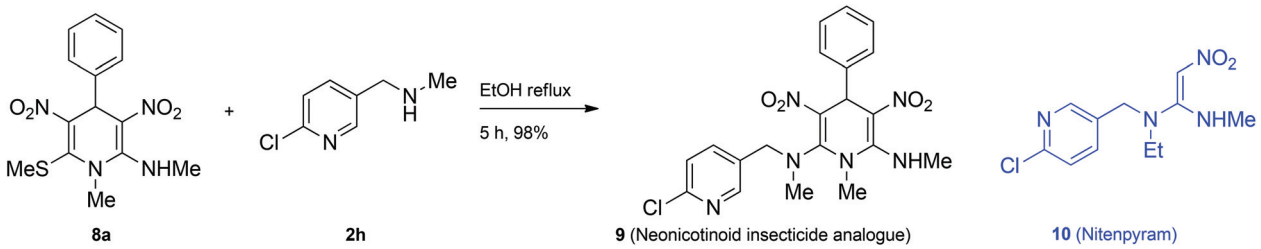


Fig. 4 Library of 1,4-DHPs **7** with diversity incorporated by replacement of C6-SMe in **8a** and **8g**.



Scheme 5 Synthesis of neonicotinoid insecticide analogue **9** from **8a**.

1,4-DHPs **7f–h** in good yields (Table 3, entries 6–8). The library of 1,4-DHPs of type **7** that was prepared in this study is shown in Fig. 4. Although it is possible to prepare dihydropyridines like **7** *via* a pseudo four-component MCR of one equivalent of primary amine, two equivalents of NMSM and one equivalent of the aldehyde, we found that the transformation is restricted to reactive and high boiling primary amines like benzyl amine. For other primary amines like butyl and hexylamine or secondary amines like piperidine the reaction was slow and low yielding.

To demonstrate an application of the present study, we designed a synthesis of neonicotinoid analogue **9** (Scheme 5). Neonicotinoids, for example nitenpyram **10** are a group of newer class of insecticides used in agriculture and flea control in domestic animals.[19] They exhibit lower toxicity in mammals than in insects compared to organochlorides, organophosphates and carbamates.[20] Although neonicotinoids have become hugely popular, there are some concerns about their activity against humans and also on human-friendly insects like honey bees.[21] Moreover acquisition of resistance to the neonicotinoid insecticides is on the rise.[22] Therefore there is a requirement to design suitable analogues with favourable properties. Chuanwen and co-workers synthesized a few 1,4-DHPs incorporating the nitenpyram structural motif and showed that when the nitro group and the secondary amine are locked in a *cis* configuration, the insecticide activity against the common pest *Aphis medicaginis* is better.[23] We have taken up synthesis of the neonicotinoid analogue **9** to demonstrate an application of our newly developed pseudo MCR for the synthesis of 1,4-DHPs. The reaction of **8a** with 1-(6-chloropyridin-3-yl)-*N*-methylmethanamine **2h** furnished the neonicotinoid analogue **9** in excellent yield. The structure of **9** was assigned on the basis of spectroscopic data and confirmed by single crystal X-ray diffraction analysis (Fig. 5, given in the Experimental section). Interestingly, the room-temperature ^{1}H NMR spectrum of **9** showed broad peaks for methylene hydrogens. On heating to 80 °C the spectrum became clear (see ESI†).

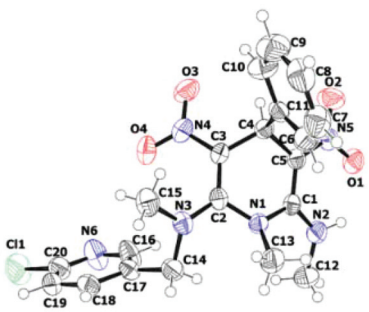


Fig. 5 ORTEP diagram of the *N*2-((6-chloropyridin-3-yl)methyl)-*N*2, *N*6,1-trimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **9**.

This result indicated slow rotation around the C2–N bond at room temperature owing to steric hindrance between $ArCH_2NMe$ and NO_2 groups.

Conclusion

In summary, we have discovered and described new pseudo three-component reactions for regio- and chemoselective, high-yielding and experimentally convenient one-pot synthesis of diversely functionalized hexa-substituted 1,4-dihydropyridines **8** from readily available aldehydes **1** and nitroketene-*N*,*S*-acetals **5**. The primary amine 2-AP acted as a tailor-made catalyst for the pseudo MCR. Conveniently the product 1,4-DHPs precipitated out of the reaction and simple filtration was enough to isolate pure products. Nucleophilic displacement of the C6 methylsulfanyl group in **8** with different primary and secondary amines afforded 1,4-dihydropyridines **7** with additional structural diversity. The newly developed protocol allowed a convenient and high-yielding synthesis of neonicotinoid insecticide analogue **9**.

Experimental

General experimental

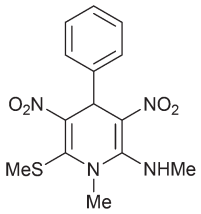
All melting points were uncorrected and were determined using open-ended capillary tubes on VEEGO VMP-DS instrument. All the reactions and chromatographic separations were observed by thin layer chromatography. Glass plates coated with silica gel (60–120 mesh SRL chemicals) were employed for thin layer chromatography (TLC). Infra Red (IR) spectra were recorded as KBr pellets on a Nicolet-6700 spectrometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for ($CDCl_3$) or (DMSO-d_6 + CCl_4, 1 : 1) solutions on a BrukerAvance 400 spectrometer with tetramethylsilane (TMS) as internal standard; *J* values are in Hz. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant, integration. High resolution mass spectra were recorded on a Water Q-TOF micro mass spectrometer using electron spray ionization mode. The X-ray diffraction measurements were performed at 298 K on Oxford CrysAlis CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). Benzaldehydes and amines was purchased from Sigma Aldrich Chemicals Private Limited and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine NMSM **5a** was gifted by Shasun Chemical Company, Chennai. We synthesized NMSM derivatives like (*E*)-*N*-benzyl-1-(methylthio)-2-nitroethenamine **5b**, (*E*)-*N*-(4-methoxyphenethyl)-1-(methylthio)-2-nitroethenamine **5c** and (*E*)-*N*-(1-(methylthio)-2-nitrovinyl)butan-1-amine **5d** in our laboratory.

General procedure for synthesis of 1,4-dihydropyridines 8

A solution of aldehydes (1.0 equiv.), NMSM (2.0 equiv.) and 2-aminopyridine (0.1 equiv.) in ethanol (3 mL) were mixed and stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography (TLC, hexanes–EtOAc, 3 : 2). The reaction mixture was cooled to room temperature and the resulting solid was filtered off and recrystallized from dichloromethane and hexane to obtain pure products **8**.

Representative procedure for preparation of hexa substituted 1,4-dihydropyridines 8a

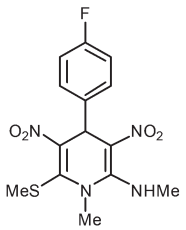
***N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine 8a.**



8a

In a round-bottomed flask a solution of benzaldehyde **1a** (105 mg, 0.94 mmol) NMSM **5a** (279 mg, 1.88 mmol) and 10 mol% of 2-aminopyridine (10 mg, 0.09 mmol) in ethanol (3 mL) were mixed and stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography (TLC, hexanes–EtOAc, 3 : 2). After 5 h yellow solid was obtained which was filtered to afford *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a**. Good crystals were obtained by recrystallization with a solution of dichloromethane–hexane (9 : 3 v/v). Yield (292 mg 92%; mp 201 °C; IR Data (ν) (KBr) 3057, 2995, 2928, 1631, 1497, 1440, 1358, 1244, 1069, 721 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.05 (s, 1H), 7.28 (t, *J* = 10.8 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 5.94 (s, 1H), 3.42 (s, 3H), 3.09 (d, *J* = 5.2 Hz, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 156.3 (C), 154.8 (C), 139.9 (C), 137.6 (C), 129.1 (CH), 127.8 (CH), 126.9 (CH), 113.2 (C), 43.2 (NMe), 40.8 (NHMe), 32.1 (CH), 16.4 (SMe); HRMS (ESI) Calcd for $C_{14}H_{16}N_4O_4SNa$ [M + Na] 359.0790 amu, found 359.0791 amu.

4-(4-Fluorophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8b.

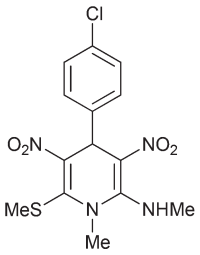


8b

Following the representative procedure, the solution of 4-fluorobenzaldehyde **1b** (202 mg, 1.62 mmol), NMSM **5a** (454 mg, 3.29 mmol) and 10 mol% of 2-aminopyridine (15 mg, 0.161 mmol in ethanol (3 mL) afforded 4-(4-fluorophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8b**. Yield (400 mg, 89%); mp 230 °C; IR Data (ν) (KBr) 3067,

2934, 1630, 1486, 1440, 1393, 1299, 1193, 1069, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.06 (s, 1H), 7.38–7.32 (m, 1H), 7.07–7.02 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.89 (td, J = 9.8, 2.9 Hz, 1H), 5.98 (s, 1H), 3.45 (s, 3H), 3.10 (d, J = 5.3 Hz, 3H), 2.56 (s, 3H),^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 162.2 (C), 155.5 (C), 142.5 (C), 136.6 (C), 130.8 (CH), 122.5 (CH), 114.4 (C), 113.7 (C), 42.8 (NMe), 39.9 (NHMe), 31.8 (CH), 16.1 (SMe); HRMS (ESI) Calcd for $C_{14}H_{15}FN_4O_4SNa$ [M + Na] 377.0696 amu, found 377.0694 amu.

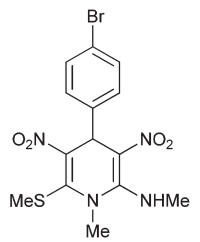
4-(4-Chlorophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8c.



8c

Following the representative procedure, the solution of 4 chlorobenzaldehyde **1c** (255 mg, 1.78 mmol), NMSM **5a** (498 mg, 3.57 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.17 mmol) in ethanol (3 mL) afforded 4-(4-chlorophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8c**. Yield (250 mg, 60%); mp 213 °C; IR Data (ν) (KBr) 3188, 3067, 2996, 2932, 1626, 1580, 1448, 1392, 1361, 1322, 1283, 1070, 778 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.05 (s, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 5.96 (s, 1H), 3.45 (s, 3H), 3.11 (d, J = 5.2 Hz, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.7 (C), 154.8 (C), 138.5 (C), 136.7 (C), 132.2 (C), 128.6 (CH), 128.4 (CH), 112.5 (C), 42.7 (NMe), 39.9 (NHMe), 31.7 (CH), 16.0 (SMe); HRMS (ESI) Calcd for $C_{14}H_{15}ClN_4O_4SNa$ [M + Na] 393.0400 amu, found 393.0400 amu.

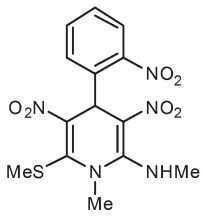
4-(4-Bromophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8d.



8d

Following the representative procedure, the solution of 4-bromo benzaldehyde **1d** (101 mg, 0.54 mmol), NMSM **5a** (173 mg, 1.08 mmol) and 10 mol% of 2-aminopyridine (12 mg, 0.05 mmol) in ethanol (3 mL) afforded 4-(4-bromophenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8d**. Yield (180 mg, 86%); mp 219 °C; IR Data (ν) (KBr) 3198, 3068, 2995, 2933, 1627, 1484, 1361, 1281, 1239, 1192, 1068, 775 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.04 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 5.94 (s, 1H), 3.44 (s, 3H), 3.10 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.7 (C), 154.8 (C), 138.9 (C), 136.6 (C), 131.6 (CH), 128.8 (CH), 120.6 (C), 112.4 (C), 42.7 (NMe), 39.9 (NHMe), 31.7 (CH), 16.0 (SMe); HRMS (ESI) Calcd for $C_{14}H_{15}BrN_4O_4SNa$ [M + Na] 436.9895 amu, found 436.9897 amu.

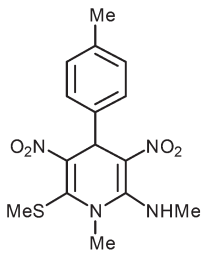
***N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-(2-nitrophenyl)-1,4-dihydropyridin-2-amine 8e.**



8e

Following the representative procedure, the solution of 2-nitrobenzaldehyde **1e** (204 mg, 1.32 mmol), NMSM **5a** (353 mg, 2.64 mmol) and 10 mol% of 2-aminopyridine (26 mg, 0.13 mmol) in ethanol (3 mL) afforded *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-(2-nitrophenyl)-1,4-dihydropyridin-2-amine **8e**. Yield (250 mg, 56%); mp 226 °C; IR Data (ν) (KBr) 2994, 2934, 1628, 1568, 1529, 1492, 1367, 1277, 1162, 1068, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.15 (s, 1H), 7.80 (dd, J = 8.0, 1.1 Hz, 1H), 7.67 (td, J = 7.9, 1.2 Hz, 1H), 7.45 (t, J = 11.5 Hz, 1H), 7.26 (dd, J = 8.0, 1.2 Hz, 1H), 6.49 (s, 1H), 3.59 (s, 3H), 3.12 (d, J = 3.1 Hz, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 156.0 (C), 152.5 (C), 149.1 (C), 136.2 (C), 133.4 (CH), 132.6 (C), 129.6 (CH), 128.8 (CH), 124.3 (CH), 112.4 (CH), 42.9 (NMe), 36.6 (NHMe), 32.0 (CH), 16.1 (SMe); HRMS (ESI) Calcd for $C_{14}H_{15}N_5O_6SNa$ [M + Na] 404.0641 amu, found 404.0639 amu.

***N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-(*p*-tolyl)-1,4-dihydropyridin-2-amine 8f.**

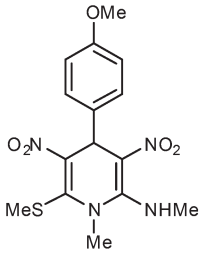


8f

Following the representative procedure, the solution of 4 methyl benzaldehyde **1f** (502 mg, 4.16 mmol), NMSM **5a** (798 mg, 8.33 mmol) and 10 mol% of 2-aminopyridine (41 mg, 0.41 mmol) in ethanol (5 mL) afforded *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-(*p*-tolyl)-1,4-dihydropyridin-2-amine **8f**. Yield (1.1 g, 75%); mp 214 °C; IR Data (ν) (KBr) 3176, 2999, 2927, 1630, 1489, 1443, 1389, 1358, 1197, 1168, 1069, 777 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 9.96 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8 Hz, 2H), 5.92 (s, 1H), 3.39 (s, 3H), 3.09

(s, 3H), 2.49 (d, J = 9.2 Hz, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.7 (C), 152.8 (C), 137.9 (C), 136.8 (C), 136.4 (C), 129.1 (CH), 126.4 (CH), 113.1 (C), 42.5 (NMe), 40.2 (NHMe), 31.6 (CH), 20.6 (CH_3), 15.9 (SMe); HRMS (ESI) Calcd for $C_{15}H_{18}N_4O_4SNa$ [M + Na] 373.0946 amu, found 373.0945 amu.

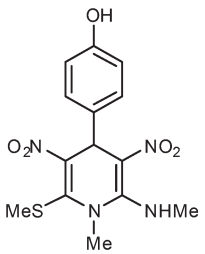
4-(4-Methoxyphenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8g.



8g

Following the representative procedure, the solution of 4-methoxybenzaldehyde **1g** (252 mg, 1.83 mmol), NMSM **5a** (531 mg, 3.67 mmol) and 10 mol% of 2-aminopyridine (21 mg, 0.18 mmol) in ethanol (3 mL) afforded 4-(4-methoxyphenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8g**. Yield (570 mg, 85%); mp 203 °C; IR Data (ν) (KBr) 3192, 2994, 2935, 1624, 1497, 1363, 1287, 1249, 1174, 1064 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 9.96 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 5.91 (s, 1H), 3.72 (s, 3H), 3.43 (s, 3H), 3.12 (d, J = 5.2 Hz, 3 H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 158.4 (C), 155.6 (C), 152.2 (C), 138.1 (C), 131.4 (CH), 127.6 (CH), 113.8 (C), 113.3 (C), 54.6 (OMe), 42.4 (NMe), 40.1 (NHMe), 31.4 (CH), 15.8 (SMe); HRMS (ESI) Calcd for $C_{15}H_{18}N_4O_5SNa$ [M + Na] 389.0896 amu, found 389.0894 amu.

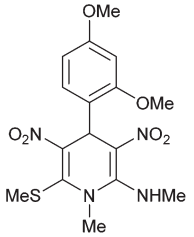
4-(1-Methyl-2-(methylamino)-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-4-yl)phenol 8h.



8h

Following the representative procedure, the solution of 4-hydroxybenzaldehyde **1h** (510 mg, 2.04 mmol), NMSM **5a** (605 mg, 4.09 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.20 mmol) in ethanol (3 mL) afforded 4-(1-methyl-2-(methylamino)-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-4-yl)phenol **8h**. Yield (240 mg, 62%); mp 221 °C; IR Data (ν) (KBr) 3244, 3014, 2940, 1624, 1511, 1478, 1394, 1353, 1322, 1278, 1239, 1195, 1162, 1122 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 9.99 (s, 1H), 9.25 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.66 (dd, J = 6.6, 1.8 Hz, 2H), 5.85 (s, 1H), 3.41 (s, 3H), 3.09 (d, J = 5.6 Hz, 3H), 2.51 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 156.8 (C), 155.8 (C), 152.6 (C), 138.3 (C), 129.8 (C), 127.6 (CH), 115.5 (CH), 113.5 (C), 42.6 (NMe), 39.7 (NHMe), 31.6 (CH), 15.9 (SMe); HRMS (ESI) Calcd for $C_{14}H_{16}N_4O_5SNa$ [M + Na] 375.0739 amu, found 375.0738 amu.

4-(2,4-Dimethoxyphenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8i.

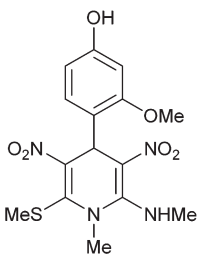


8i

Following the representative procedure, the solution of 2,4-dimethoxy benzaldehyde **1i** (501 mg, 3.01 mmol), NMSM **5a** (891 mg, 6.02 mmol) and 10 mol% of 2-aminopyridine (25 mg, 6.02 mmol) in ethanol (5 mL) afforded 4-(2,4-dimethoxyphenyl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8i**. Yield (1.1 g, 88%); mp 204 °C; IR Data (ν) (KBr) 3165, 2959, 2836, 1628, 1485, 1391, 1362, 1205, 1165, 1047, 770 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.12 (s, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.4, 2.3 Hz, 1H) 5.86 (s, 1H), 3.73 (s, 3 H), 3.70 (s, 3H), 3.38 (s, 3H), 3.12 (d, J = 5.2 Hz, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 159.9 (C), 158.1 (C), 156.8 (C), 148.3 (C), 137.9 (C), 129.5 (CH), 118.4 (C), 111.3 (C), 104.4 (CH), 98.8 (CH), 55.3 (OMe), 54.9 (OMe), 41.8 (NMe), 37.9 (NHMe), 31.8 (CH), 15.6 (SMe); HRMS (ESI) Calcd for $C_{16}H_{20}N_4O_6SNa$ [M + Na] 419.1001 amu, found 419.1002 amu.

Empirical formula, $C_{16}H_{20}N_4O_6S$; formula weight, 396.41; crystal colour, light yellow; crystal dimensions a = 7.6554(3) Å, b = 9.9905(4) Å, c = 12.4133(5) Å; α = 84.570(4), β = 88.088(3), γ = 67.987(4); crystal system, triclinic; V = 876.22(7) A^3; space group $P\bar{1}$; Z = 2; D_{calcd} = 1.495 g cm^{-3}; $F_{(000)}$ = 414.0; $R(I \geq 2\sigma_1)$ = 0.1010, wR^2 = 0.2675. Detailed X-ray crystallographic data was available from the Cambridge Crystallographic Data Centre (for compound **8i** CCDC 992572; see Fig. 2).

3-Methoxy-4-(1-methyl-2-(methylamino)-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-4-yl)phenol 8j.

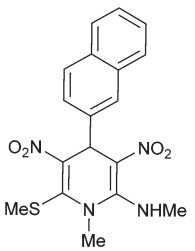


8j

Following the representative procedure, the solution of 4-hydroxy-2-methoxybenzaldehyde **1j** (502 mg, 3.28 mmol),

NMSM **5a** (973 mg, 6.57 mmol) and 10 mol% of 2-aminopyridine (30 mg, 0.32 mmol) in ethanol (5 mL) afforded 3-methoxy-4-(1-methyl-2-(methylamino)-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-4-yl)phenol **8j**. Yield (980 mg, 82%); mp 229 °C; IR Data (ν) (KBr) 3442, 3014, 2934, 1629, 1484, 1445, 1363, 1324, 1241, 1193, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.03 (s, 1H), 8.84 (s, 1H), 6.68 (d, J = 8 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 6.50 (dd, J = 8, 1.6 Hz, 1H), 5.90 (s, 1H), 3.74 (s, 3H) 3.44(s, 3H), 3.12 (d, J = 5.2 Hz, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 153.3 (C), 147.5 (C), 146.1 (C), 137.9 (C), 130.4 (CH), 118.8 (CH), 115.5 (C), 113.2 (CH), 110.7 (C), 55.4 (OMe), 42.6 (NMe), 39.9 (NHMe), 31.6 (CH), 15.9 (SMe); HRMS (ESI) Calcd for $C_{15}H_{18}N_4O_6SNa$ [M + Na] 405.0845 amu, found 405.0847 amu.

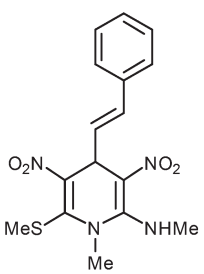
***N*,1-Dimethyl-6-(methylthio)-4-(naphthalen-2-yl)-3,5-dinitro-1,4-dihydropyridin-2-amine 8k.**



8k

Following the representative procedure, the solution of 2-naphthaldehyde **1k** (501 mg, 3.20 mmol) NMSM **5a** (948 mg, 6.41 mmol) and 10 mol% of 2-aminopyridine (30 mg, 0.32 mmol) and in ethanol (5 mL) afforded *N*,1-dimethyl-6-(methylthio)-4-(naphthalen-2-yl)-3,5-dinitro-1,4-dihydropyridin-2-amine **8k**. Yield (1.1 g, 90%); mp 217 °C; IR Data (ν) (KBr) 3421, 3200, 3049, 2928, 1629, 1576, 1481, 1446, 1370, 1290, 1245, 1195, 1068 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.11 (s, 1H), 7.87 (dd, J = 21.8, 7.9 Hz, 3H), 7.63 (s, 1H), 7.47 (dd, J = 9.1, 5.3 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 6.20 (s, 1H), 3.50 (s, 3H), 3.14 (d, J = 3.9 Hz, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.9 (C), 154.7 (C), 137.2 (C), 137.1 (C), 132.8 (C), 132.2 (C), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.2 (CH), 125.9 (CH), 125.1 (CH), 124.9 (CH), 112.8 (C), 42.8 (NMe), 40.6 (CH), 31.8 (NHMe), 16.1 (SMe); HRMS (ESI) Calcd for $C_{18}H_{18}N_4O_4SNa$ [M + Na] 409.0946 amu, found 409.0946 amu.

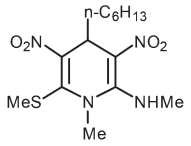
***(E)*-*N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-styryl-1,4-dihydropyridin-2-amine 8l.**



8l

Following the representative procedure, the solution of cinnamaldehyde **1l** (203 mg, 1.51 mmol), NMSM **5a** (448 mg, 3.03 mmol) and 10 mol% of 2-aminopyridine (14 mg, 0.15 mmol) in ethanol (5 mL) afforded (*E*)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-styryl-1,4-dihydropyridin-2-amine **8l**. Yield (400 mg, 73%); mp 206 °C; IR Data (ν) 3436, 3241, 3009, 2926, 1621, 1549, 1511, 1442, 1390, 1360, 1270, 1244, 1190, 1115 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.02 (s, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 10.8 Hz, 2H). 7.20 (t, J = 10.4 Hz, 1H), 6.36 (d, J = 15.6 Hz, 1H), 6.05 (dd, J = 15.6, 6.8 Hz, 1H), 5.48 (d, J = 6.8 Hz, 1H), 3.44 (s, 3H), 3.20 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 155.0 (C), 136.2 (C), 135.9 (C), 130.2 (CH), 128.2 (CH), 127.5 (CH), 126.3 (CH), 125.8 (CH), 119.9 (C), 42.6 (NMe), 38.4 (NHMe), 31.4 (CH), 15.7 (SMe); HRMS (ESI) Calcd for $C_{16}H_{18}N_4O_4SNa$ [M + Na] 385.0946 amu, found 385.0942 amu.

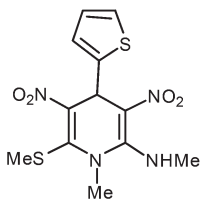
***N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-pentyl-1,4-dihydropyridin-2-amine 8m.**



8m

Following the representative procedure, the solution of hexanaldehyde **1m** (101 mg, 1.00 mmol), NMSM **5a** (296 mg, 2.00 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.20 mmol) in ethanol (3 mL) afforded *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-pentyl-1,4-dihydropyridin-2-amine **8m**. Yield (220 mg, 64%); mp 195 °C; IR Data (ν) 3445, 3202, 3167, 2928, 2851, 1629, 1491, 1442, 1353, 1322, 1240, 1193, 1167, 1102, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (d, J = 4.8 Hz, 1H), 4.97 (t, J = 9.2 Hz, 1H), 3.36 (s, 3H), 3.12 (d, J = 5.2 Hz, 3H), 2.44 (s, 3H), 1.48–1.42 (m, 2H), 1.23–1.11 (m, 6H), 0.82 (t, J = 11.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (C), 150.3 (C), 139.9 (C), 114.9 (C), 42.6 (NMe), 36.2 (NHMe), 34.2 (CH_2), 31.7 (CH_2), 31.5 (CH), 25.6 (CH_2), 22.6 (CH_2), 16.4 (SMe), 14.1 (Me); HRMS (ESI) Calcd for $C_{13}H_{22}N_4O_4SNa$ [M + Na] 353.1259 amu, found 353.1258 amu.

***N*,1-Dimethyl-6-(methylthio)-3,5-dinitro-4-(thiophen-2-yl)-1,4-dihydropyridin-2-amine 8n.**

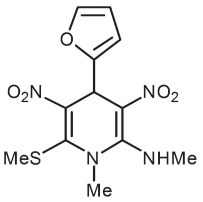


8n

Following the representative procedure, the solution of thiophene-2-carbaldehyde **1n** (202 mg, 1.78 mmol) NMSM **5a** (501 mg, 3.56 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.17 mmol) in ethanol (3 mL) afforded *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-(thiophen-2-yl)-1,4-dihydropyridin-

2-amine **8n**. Yield (410 mg, 70%); mp 209 °C; IR Data (ν) (KBr) 3419, 3196, 2994, 2927, 1627, 1576, 1480, 1427, 1392, 1363, 1287, 1158, 1066, 812 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 9.98 (s, 1H), 7.32 (dd, J = 5.0, 1.2 Hz, 1H), 6.92 (dd, J = 5.10, 3.5 Hz, 1H), 6.83 (t, 2.1 Hz, 1H), 6.21 (s, 1H), 3.40 (s, 3H), 3.10 (d, J = 4.9 Hz, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.5 (C), 143.1 (C), 136.6 (C), 126.9 (CH), 124.8 (CH), 124.2 (CH), 112.9 (C), 42.7 (NMe), 36.1 (CH), 31.7 (NHMe), 16.0 (SMe); HRMS (ESI) Calcd for $C_{12}H_{14}N_4O_4S_2Na$ [M + Na] 365.0354 amu, found 365.0354 amu.

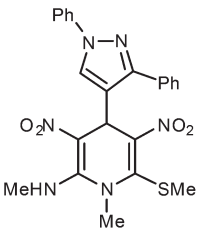
4-(Furan-2-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8o.



8o

Following the representative procedure, the solution of furfuraldehyde **1o** (502 mg, 5.31 mmol), NMSM **5a** (801 mg, 10.63 mmol) and 10 mol% of 2-aminopyridine (49 mg, 0.53 mmol) in ethanol (5 mL) afforded 4-(furan-2-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8o**. Yield (990 mg, 90%); mp 200 °C; IR Data (ν) Data 3197, 3110, 2945, 1635, 1569, 1569, 1487, 1442, 1393, 1301, 1278, 1156, 1066, 1010, 777 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 9.95 (s, 1H), 7.46 (s, 1H), 6.32 (s, 1H), 6.16 (s, 1H), 6.05 (s, 1H), 3.38 (s, 3H), 3.12 (d, J = 2.4 Hz, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 155.1 (C), 150.7 (C), 142.2 (C), 135.0 (CH), 110.72 (CH), 110.2 (CH), 106.1 (C), 42.4 (NMe), 34.8 (NHMe), 31.3 (CH), 15.8 (SMe); HRMS (ESI) Calcd for $C_{12}H_{14}N_4O_5SNa$ [M + Na] 349.0583 amu, found 349.0582 amu.

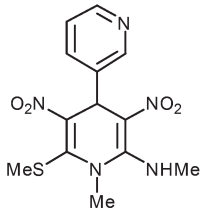
4-(1,3-Biphenyl-1*H*-pyrazol-4-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8p.



8p

Following the representative procedure, the solution of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1p** (101 mg, 0.40 mmol), NMSM **5a** (202 mg, 0.80 mmol) and 10 mol% of 2-aminopyridine (7 mg, 0.040 mmol) in ethanol (3 mL) afforded 4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8p**. Yield (110 mg, 78%); mp 216 °C; IR Data (ν) (KBr) 3125, 1622, 1534, 1493, 1450, 1372, 1300, 1276, 1242, 1174, 1202, 1118, 1065, 785 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.10 (s, 1H), 8.12 (s, 1H), 7.83 (dd, J = 8.6, 1.0 Hz, 2H), 7.69–7.67 (m, 2H), 7.47–7.43 (m, 5H), 7.28 (t, J = 11.1 Hz, 1H), 6.18 (s, 1H), 3.46 (s, 3H), 3.08 (d, J = 5.2 Hz, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.7 (C), 152.1 (C), 150.9 (C), 139.2 (C), 137.7 (C), 133.3 (C), 129.1 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 126.1 (CH), 120.4 (C), 118.4 (CH), 112.9 (C), 41.9 (NMe), 39.9 (NHMe), 31.8 (CH), 15.9 (SMe); HRMS (ESI) Calcd for $C_{23}H_{22}N_6O_4SNa$ [M + Na] 501.1321 amu, found 501.1321 amu.

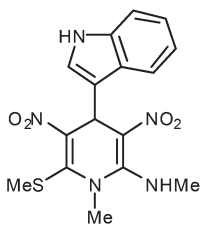
***N*,1′-Dimethyl-6′-(methylthio)-3′,5′-dinitro-1′,4′-dihydro-[3,4′-bipyridin]-2′-amine 8q.**



8q

Following the representative procedure, the solution of pyridine-3-carbaldehyde **1q** (251 mg, 2.35 mmol), NMSM **5a** (501 mg, 4.71 mmol) and 10 mol% of 2-aminopyridine (31 mg, 0.23 mmol) in ethanol (3 mL) afforded *N*,1′-dimethyl-6′-(methylthio)-3′,5′-dinitro-1′,4′-dihydro-[3,4′-bipyridin]-2′-amine **8q**. Yield (600 mg, 76%); mp 149 °C; IR Data (ν) (KBr) 3443, 3204, 3069, 2931, 2810, 2742, 1693, 1631, 1476, 1446, 1394, 1299, 1281, 794 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.09 (s, 1H), 8.43 (td, J = 7.9, 1.9 Hz, 2H), 7.56–7.53 (m, 1H), 7.34–7.30 (m, 1H), 5.94 (s, 1H), 3.52 (s, 3H), 3.14 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 155.5 (C), 148.4 (C), 148.2 (C), 136.1 (CH), 135.1 (CH), 134.4 (CH), 123.7 (CH), 112.1 (C), 42.9 (NMe), 40.1 (NHMe), 31.7 (CH), 16.1 (SMe); HRMS (ESI) Calcd for $C_{13}H_{15}N_5O_4SNa$ [M + Na] 360.0742 amu, found 360.0744 amu.

4-(1*H*-indol-3-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine 8r.

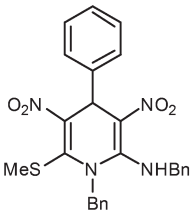


8r

Following the representative procedure, the solution of indole-3-carbaldehyde **1r** (101 mg, 0.68 mmol), NMSM **5a** (202 mg, 1.37 mmol) and 10 mol% of 2-aminopyridine (12 mg, 0.06 mmol) in ethanol (3 mL) afforded 4-(1*H*-indol-3-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine **8r**. Yield (180 mg, 69%); mp 229 °C; IR Data (ν) (KBr) 3419,

1619, 1456, 1364, 1230, 1166, 1114, 780 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.93 (s, 1H), 9.93 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.06 (t, 16.7 Hz, 1H), 6.98–6.92 (m, 2H), 6.28 (s, 1H), 3.40 (s, 3H), 3.08 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 156.0 (C), 152.5 (C), 138.5 (C), 136.5 (CH), 125.4 (C), 122.0 (C), 121.3 (CH), 118.9 (CH), 118.8 (CH), 114.4 (C), 113.4 (C), 111.5 (CH), 41.9 (NMe), 39.9 (NHMe), 31.8 (CH), 15.9 (SMe); HRMS (ESI) Calcd for $C_{16}H_{17}N_5O_4SNa$ [M + Na] 398.0899 amu, found 398.0898 amu.

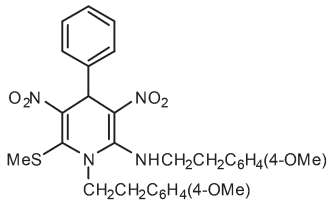
***N*,1-Dibenzyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine 8s.**



8s

Following the representative procedure, the solution of benzaldehyde **1a** (102 mg, 0.94 mmol), (*E*)-*N*-benzyl-1-(methylthio)-2-nitroethenamine **5b** (402 mg, 1.88 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.09 mmol) in ethanol (3 mL) afforded *N*,1-dibenzyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8s**. Yield (250 mg, 84%); mp 224 °C; IR Data (ν) 3060, 3033, 2924, 1614, 1415, 1376, 1294, 1133, 963, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (t, J = 8.4 Hz, 1H), 7.44–7.36 (m, 5H), 2.26 (s, 1H), 7.15–7.03 (m, 5H), 6.94 (t, J = 11.6 Hz, 2H), 6.43 (d, J = 7.2 Hz, 2H), 6.16 (s, 1H), 5.08 (d, J = 14.4 Hz, 1H), 4.87 (d, J = 14.4 Hz, 1H), 4.73–4.71 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (C), 146.6 (C), 140.9 (C), 138.4 (C), 136.0 (C), 133.8 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.8 (C), 128.6 (CH), 127.1 (CH), 126.9 (CH), 117.2 (C), 56.9 (CH_2), 50.4 (CH_2), 41.3 (CH), 16.9 (SMe); HRMS (ESI) Calcd for $C_{26}H_{24}N_4O_4SNa$ [M + Na] 511.1416 amu, found 511.1418 amu.

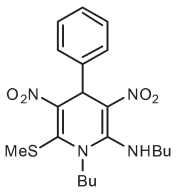
***N*,1-Bis(4-methoxyphenethyl)-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine 8t.**



8t

Following the representative procedure, the solution of benzaldehyde **1a** (202 mg, 1.88 mmol), (*E*)-*N*-(4-methoxyphenethyl)-1-(methylthio)-2-nitroethenamine **5c** (501 mg, 3.77 mmol) and 10 mol% of 2-aminopyridine (42 mg, 0.37 mmol) in ethanol (3 mL) afforded *N*,1-bis(4-methoxyphenethyl)-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8t**. Yield (550 mg, 86%); mp 210 °C; IR Data (ν) 3128, 3064, 2997, 2935, 1634, 1487, 1359, 1282, 1067, 818, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + CCl_4, 1 : 1) δ 9.81 (s, 1H), 7.26–6.75 (m, 13H) 6.40 (s, 1H),3.80 (td, J = 18.3, 4.94 Hz, 1H), 3.60 (d, J = 10.8 Hz, 6H), 3.53–3.50 (m, 3H), 2.94–2.90 (m, 2H), 2.38 (s, 3H), 2.18 (td, J = 18, 4.98 Hz, 1H), 1.94 (dd, J = 17.5, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4, 1 : 1) δ 159.0 (C), 158.8 (C), 154.6 (C), 139.9 (C), 139.6 (C), 129.8 (CH), 129.5 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 126.3 (CH), 116.1 (CH), 114.6 (CH), 114.3 (CH), 55.5 (OMe), 55.4 (OMe), 55.4 (CH_2), 48.3 (CH_2), 40.1 (CH_2), 36.0 (CH_2), 34.3 (CH), 17.2 (SMe); HRMS (ESI) Calcd for $C_{30}H_{32}N_4O_6SNa$ [M + Na] 599.6940 amu, found 599.1942 amu.

***N*,1-Dibutyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine 8u.**



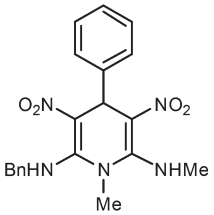
8u

Following the representative procedure, the solution of benzaldehyde **1a** (101 mg, 0.94 mmol), (*E*)-*N*-(1-(methylthio)-2-nitrovinyl)butan-1-amine **5d** (322 mg, 1.88 mmol) and 10 mol% of 2-aminopyridine (20 mg, 0.18 mmol) in ethanol (3 mL) afforded *N*,1-dibutyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8u**. Yield (220 mg, 70%); mp 225 °C; IR Data (ν) 3445, 2962, 2929, 2872, 1623, 1493, 1422, 1372, 1237, 1207, 1182, 1160, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, J = 3.6 Hz, 1H), 7.26–7.20 (m, 3H), 7.06–7.04 (dd, J = 7.3, 1.0 Hz, 2H), 6.41 (s, 1H), 3.74–3.34 (m, 1H), 3.33–3.32 (m, 2H), 3.30–3.27 (m, 1H), 2.42 (s, 3H), 1.72–1.46 (m, 2H), 1.46 (s, 1H), 1.46–1.44 (m, 2H), 1.03–0.94 (m, 6H), 0.64 (t, J = 10.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (C), 149.6 (C), 139.99 (C), 139.91 (C), 128.8 (CH), 127.6 (CH), 126.4 (CH), 115.9 (C), 54.2 (CH_2), 46.9 (CH_2), 40.0 (NMe), 32.2 (CH_2), 31.0 (CH_2), 19.9 (CH_2), 19.8 (CH_2), 16.9 (SMe), 13.6 (Me), 13.3 (Me); HRMS (ESI) Calcd for $C_{20}H_{28}N_4O_4SNa$ [M + Na] 443.1729 amu, found 443.1729 amu.

General procedure for synthesis of 1,4-dihydropyridine 7

A solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine (1 equiv.) and aliphatic amine (1 equiv.) in ethanol (5 mL) were mixed and stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography (TLC). The reaction mixture was cooled to room temperature and the resulting solid was filtered off and recrystallized from dichloromethane and hexane to obtain pure products 7.

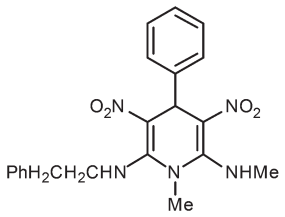
***N*2-Benzyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 7a.**



7a

In a round-bottomed flask a solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (502 mg, 1.48 mmol) and benzyl amine **2a** (159 mg, 1.48 mmol) in ethanol (5 mL) were mixed and stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography (TLC, hexanes–EtOAc, 2 : 3). After 1 h white solid was obtained which was filtered to afford *N*2-benzyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **7a**. Yield (510 mg, 98%); mp 218 °C; IR Data (ν) 3023, 2995, 2945, 2837, 1639, 1504, 1463, 1375, 1287, 1155, 1052, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.44 (s, 1H), 10.20 (s, 1H), 7.41–7.38 (m, 4H), 7.35 (d, J = 3.4 Hz, 1H), 7.33–7.25 (m, 2H), 7.21 (t, J = 12.3 Hz, 3H), 5.90 (s, 1H), 4.78–4.72 (m, 2H), 3.38 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 155.2 (C), 141.5 (C), 136.8 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.3 (CH), 126.8 (CH), 126.7 (CH), 114.8 (C), 114.1 (C), 48.5 (NMe), 42.2 (CH_2), 38.5 (CH), 31.7 (NHMe); HRMS (ESI) Calcd for $C_{20}H_{21}N_5O_4Na$ [M + Na] 418.1491 amu, found 418.1494 amu.

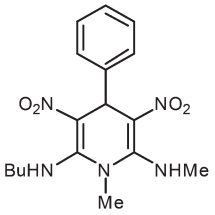
***N*2,1-Dimethyl-3,5-dinitro-*N*6-phenethyl-4-phenyl-1,4-dihydropyridine-2,6-diamine 7b.**



7b

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (501 mg, 1.48 mmol) and phenylethyl amine **2b** (182 mg, 1.48 mmol) in ethanol (5 mL) afforded *N*2,1-dimethyl-3,5-dinitro-*N*6-phenethyl-4-phenyl-1,4-dihydropyridine-2,6-diamine **7b**. Yield (600 mg, 90%). mp 220 °C; IR Data (ν) 3607, 3518, 1493, 1450, 1408, 1377, 737 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.18 (s, 1H), 10.08 (s, 1H), 7.29–7.26 (m, 4H), 7.24 (d, J = 1.2 Hz, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.13 (d, J = 7.2 Hz, 2H), 5.83 (s, 1H), 3.75–3.74 (m, 2H), 3.28 (s, 3H), 3.01 (s, 3H), 2.50–2.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 155.8 (C), 155.5 (C), 141.5 (C), 137.8 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 114.5 (C), 113.8 (C), 46.8 (CH_2), 43.1 (NMe), 40.2 (CH_2), 38.4 (CH), 35.6 (NHMe); HRMS (ESI) Calcd for $C_{21}H_{23}N_5O_4Na$ [M + Na] 432.1648 amu, found 432.1648 amu.

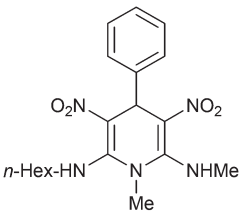
***N*2-Butyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 7c.**



7c

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (202 mg, 0.59 mmol) and butyl amine **2c** (43 mg, 0.59 mmol) in ethanol (3 mL) afforded *N*2-butyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **7c**. Yield (180 mg, 81%); mp 215 °C; IR Data (ν) 3148, 2954, 2868, 1638, 1498, 1466, 1369, 1284, 1284, 1159, 1052, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (d, J = 4.4 Hz, 2H), 7.26–7.17 (m, 5H), 6.01 (s, 1H), 3.45–3.29 (m, 4H), 2.98 (d, J = 5.2 Hz, 3H), 1.70–1.65 (m, 3H), 1.46–1.40 (m, 2H), 0.95 (t, J = 10.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4, 1 : 1) δ 156.2 (C), 155.4 (C), 140.9 (C), 128.7 (CH), 127.42 (CH), 127.40 (CH), 116.0 (C), 115.9 (C), 45.6 (NMe), 42.6 (CH_2), 38.9 (CH_2), 31.9 (CH), 31.7 (CH_2), 20.1 (NHMe), 13.7 (Me); HRMS (ESI) Calcd for $C_{17}H_{23}N_5O_4Na$ [M + Na] 384.1648 amu, found 384.1646 amu.

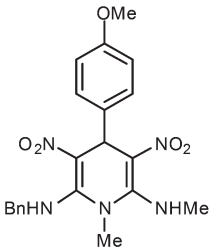
***N*2-Hexyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 7d.**



7d

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (251 mg, 0.74 mmol) and hexylamine **2d** (76 mg, 0.74 mmol) in ethanol (3 mL) afforded *N*2-hexyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **7d**. Yield (250 mg, 80%); mp 208 °C; IR Data (ν) 3146, 3007, 2930, 2859, 1641; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 2H), 7.33 (d, J = 4 Hz, 2H), 7.27 (d, J = 4 Hz, 3H), 6.09 (s, 1H), 3.50–3.39 (m, 4H), 3.06 (d, J = 4.8 Hz, 3H), 1.78–1.73 (m, 3H), 1.48–1.33 (m, 6H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4, 1 : 1) δ 156.2 (C), 155.3 (C), 140.9 (C), 128.7 (CH), 127.42 (CH), 127.40 (CH), 116.0 (C), 115.9 (CH), 45.9 (NMe), 42.5 (CH_2), 38.9 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 26.6 (NHMe), 22.5 (CH_2), 14.1 (Me); HRMS (ESI) Calcd for $C_{19}H_{27}N_5O_4Na$ [M + Na] 412.1961 amu, found 412.1960 amu.

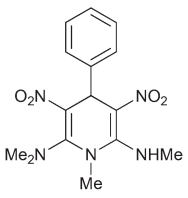
***N*2-Benzyl-4-(4-methoxyphenyl)-*N*6,1-dimethyl-3,5-dinitro-1,4-dihydropyridine-2,6-diamine 7e.**



7e

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (102 mg, 0.27 mmol) benzyl amine **2a** (35 mg, 0.27 mmol) in ethanol (2 mL) afforded *N*2-benzyl-4-(4-methoxyphenyl)-*N*6,1-dimethyl-3,5-dinitro-1,4-dihydropyridine-2,6-diamine **7e**. Yield (120 mg, 96%); mp 198 °C; IR Data (ν) 3444, 3002, 2952, 2923, 1638, 1507, 1469, 1370, 1161, 1194, 1054, 779 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + CCl_4, 1 : 1) δ 10.41 (s, 1H), 10.17 (s, 1H), 7.40–7.31 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.82 (s, 1H), 4.78–4.66 (m, 2H), 3.71 (s, 3H), 3.37 (s, 3H), 3.23 (s, 3H), 2.93 (d, J = 5.2 Hz, 3H); ^{13}C NMR (DMSO-d_6 + CCl_4, 1 : 1) δ 158.1 (C), 155.7 (C), 155.1 (C), 136.8 (C), 133.3 (C), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 115.0 (CH), 114.3 (C), 113.7 (C), 54.9 (OMe), 48.4 (CH_2). 42.1 (NMe), 37.7 (CH), 31.6 (NHMe). HRMS (ESI) Calcd for $C_{21}H_{23}N_5O_5Na$ [M + Na] 448.1597 amu, found 448.1594 amu.

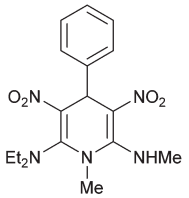
***N*2,*N*2,*N*6,1-Tetramethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 7f.**



7f

In a round-bottomed flask a solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (201 mg, 0.59 mmol) and *N*,*N*-dimethylamine **2e** (24 mg, 1.48 mmol) in ethanol (3 mL) were mixed and stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography (TLC, hexanes–EtOAc, 2 : 3). After 5 h yellow solid was obtained which was filtered to afford *N*2,*N*2,*N*6, 1-tetramethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **7f**. Yield (220 mg, 92%); mp 220 °C; IR Data (ν) 3023, 2995, 2945, 2837, 1639, 1504, 1463, 1375, 1287, 1155, 1052, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.0 (s, 1H), 3.33 (s, 3H), 3.11 (d, J = 4.8 Hz, 3H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4 (C), 156.3 (C), 142.4 (C), 128.7 (CH), 126.8 (CH), 125.8 (CH), 116.4 (C), 114.2 (C), 40.8 (NMe), 40.15 (CH), 32.06 (NHMe), 39.52 (Me); HRMS (ESI) Calcd for $C_{15}H_{19}N_5O_4Na$ [M + Na] 356.1335 amu, found 356.1338 amu.

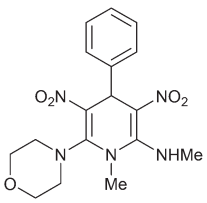
***N*2,*N*2-Diethyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 7g.**



7g

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (202 mg, 0.59 mmol) and *N*,*N*-diethylamine **2f** (44 mg, 0.59 mmol) in ethanol (3 mL) afforded *N*2,*N*2-diethyl-*N*6,1-dimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **7g**. Yield (200 mg, 90%); mp 215 °C; IR Data (ν) 3025, 3000, 2982, 2840, 1666, 1516, 1472, 1386, 1290, 1170, 1062, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.30–7.25 (m, 2H), 7.22–7.18 (m, 2H), 7.16–7.12 (m, 2H), 5.98 (s, 1H), 3.44–3.35 (m, 4H), 3.34 (s, 3H), 3.12 (s, 3H), 3.10 (s, 3H), 1.10 (d, J = 6.9 Hz, 6H); (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.0 (s, 1H), 3.33 (s, 3H), 3.11 (d, J = 4.8 Hz, 3H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4 (C), 156.2 (C), 142.0 (C), 128.6 (CH), 126.8 (CH), 125.9 (CH), 116.3 (C), 113.8 (C), 45.1 (CH_2), 40.7 (NMe), 32.1 (NHMe), 31.9 (CH), 13.6 (Me); HRMS (ESI) Calcd for $C_{17}H_{23}N_5O_4Na$ [M + Na] 384.1648 amu, found 384.1648 amu.

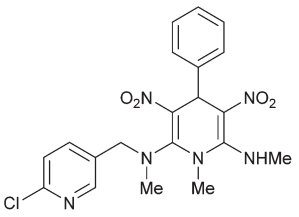
***N*,1-Dimethyl-6-morpholino-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine 7h.**



7h

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (102 mg, 0.95 mmol) and morpholine **2g** (75 mg, 0.95 mmol) in ethanol (3 mL) afforded *N*, 1-dimethyl-6-morpholino-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **7h**. Yield (140 mg, 81%); mp 222 °C; IR Data (ν) 3045, 3010, 2988, 2870, 1666, 1520, 1488, 1396, 1289, 1172, 1080, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.31–7.27(m, 2H), 7.22–7.21 (m, 1H), 7.17–7.13 (m, 2H), 5.96 (s, 1H), 3.82–3.35 (s, 6H), 3.33(s, 3H), 3.1 (d, J = 5.4 Hz, 3H), 3.13 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2 (C), 142.9 (C), 128.7 (CH), 128.4 (CH), 126.8 (CH), 125.9 (CH), 116.3 (C), 113.8 (C), 65.3 (CH_2), 54.9 (CH_2), 41.3 (NMe), 39.5(CH), 32.1 (NHMe); HRMS (ESI) Calcd for $C_{17}H_{21}N_5O_5Na$ [M + Na] 398.1440 amu, found 398.1441 amu.

***N*2-((6-Chloropyridin-3-yl)methyl)-*N*2,*N*6,1-trimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine 9.**



9

Following the representative procedure, the solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **8a** (101 mg, 0.30 mmol) and 1-(6-chloropyridin-3-yl)-*N*-methylmethanamine **2h** (52 mg, 0.30 mmol) in ethanol (3 mL) afforded *N*2-((6-chloropyridin-3-yl)methyl)-*N*2,*N*6,1-trimethyl-3,5-dinitro-4-phenyl-1,4-dihydropyridine-2,6-diamine **9**. Yield (120 mg, 98%); mp 231 °C; IR Data (ν) 3023, 2926, 1628, 1593, 1454, 1388, 1344, 1245, 1166, 1111, 1047, 931, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.31 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.40 (dd, J = 8.4 Hz, 1H), 7.29–7.20 (m, 3H), 7.12 (d, J = 7.6 Hz, 2H), 5.99 (s, 1H), 4.54 (d, J = 14.8 Hz, 1H), 4.41 (d, J = 14.8 Hz, 1H), 3.10 (d, J = 7.2 Hz, 6H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5 (C), 156.7 (C), 156.0(C), 150.0 (C), 149.9 (C), 142.2 (C), 140.3 (CH), 130.5 (CH), 128.7 (CH), 126.8 (CH), 125.8 (CH), 124.1 (CH), 116.2 (C), 54.2 (CH_2), 53.4 (NMe), 40.8 (NMe), 39.1 (CH), 32.2 (NMe); HRMS (ESI) Calcd for $C_{20}H_{21}ClN_6O_4Na$ [M + Na] 467.1211 amu, found 467.1211 amu.

Empirical formula, $C_{20}H_{21}ClN_6O_4$; formula weight, 444.8715; crystal colour, light yellow; crystal dimensions a = 11.9749(6) Å, b = 15.2082(6) Å, c = 12.0561(8) Å; α = 90, β = 106.909(6), γ = 90; crystal system, monoclinic; V = 2100.7(2) A^3; space group $P2_1/c$; Z = 4; D_{calcd} = 1.406 g cm^{-3}; $F_{(000)}$ = 928.0; $R(I \geq 2\sigma_1)$ = 0.0423, wR^2 = 0.1404. Detailed X-ray crystallographic data was available from the Cambridge Crystallographic Data Centre (for compound **9** CCDC 918142).

Acknowledgements

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References

1 (*a*) L. F. Tietze, G. Brasche and K. Gericke, in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (*b*) J. Zhu and H. Bienaymé, in *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005.

2 (*a*) S. Ali and B. A. H. Pourasad, *J. Chem. Res.*, 2014, **38**, 62–63; (*b*) F.-L. Yang, F.-X. Wang, T.-T. Wang, Y.-J. Wang and S.-K. Tian, *Chem. Commun.*, 2014, **50**, 2111–2113; (*c*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168–3210; (*d*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17–89; (*e*) H. L. Wei, Z. Y. Yan, Y. L. Niu, G. Q. Li and Y. M. Liang, *J. Org. Chem.*, 2007, **72**, 8600–8603; (*f*) X. H. Duan, X. Y. Liu, L. N. Guo, M. C. Liao, W. M. Liu and Y. M. Liang, *J. Org. Chem.*, 2005, **70**, 6980–6983; (*g*) B. Jiang, S. J. Tu, P. Kaur, W. Wever and G. G. Li, *J. Am. Chem. Soc.*, 2009, **131**, 11660–11661; (*h*) B. Jiang, T. Rajale, W. Wever, S. J. Tu and G. G. Li, *Chem. – Asian J.*, 2010, **5**, 2318–2335; (*i*) C. Cheng, B. Jiang, S. J. Tu and G. G. Li, *Green Chem.*, 2011, **13**, 2107–2115; (*j*) X. F. Lin, Z. J. Mao, X. X. Dai, P. Lu and Y. G. Wang, *Chem. Commun.*, 2011, **47**, 6620–6622; (*k*) D. Hong, Y. X. Zhu, Y. Li, X. F. Lin, P. Lu and Y. G. Wang, *Org. Lett.*, 2011, **13**, 4668–4671; (*l*) Y. X. Zhu, G. W. Yin, D. Hong, P. Lu and Y. G. Wang, *Org. Lett.*, 2011, **13**, 1024–1027.

3 (*a*) A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1–82; (*b*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223–243; (*c*) C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937–7168.

4 (*a*) Y. Sambongi, H. Nitta, K. Ichihashi, M. Futai and I. Ueda, *J. Org. Chem.*, 2002, **67**, 3499–3501; (*b*) T. Itoh, K. Nagata, A. Kurihara, M. Miyazaki and A. Ohsawa, *Tetrahedron Lett.*, 2002, **43**, 3105–3108.

5 (*a*) G. Swarnalatha, G. Prasanthi, N. Sirisha and C. M. Chetty, *Int. J. ChemTech Res.*, 2011, **3**, 75–89; (*b*) A. Boumendjel, H. Baubichon-Cortay, D. Trompier, T. Perrotton and A. Di Pietro, *Med. Res. Rev.*, 2005, **25**, 453–472; (*c*) A. Hilgeroth, *Med. Chem.*, 2002, **2**, 235–245; (*d*) G. Prasanthi, K. V. S. R. G. Prasad and K. Bharathi, *Eur. J. Med. Chem.*, 2014, **73**, 97–104.

6 J. T. David, *Biochem. Pharmacol.*, 2007, **74**, 1–9.

7 R. Boer and V. Gekeler, *Drugs Future*, 1995, **20**, 499–509.

8 (*a*) V. M. Briukhanov, *Exp. Clin. Pharmacol.*, 1994, **57**, 47–49; (*b*) S. Bahekar and D. Shinde, *Acta Pharm. A*, 2002, **52**, 281–287.

9 (*a*) N. Edraki, A. R. Mehdipour, M. Khoshneviszadeh and R. Miri, *Drug Discovery Today*, 2009, **14**, 1058–1066; (*b*) F. Bossert and W. Vater, *Med. Chem. Rev.*, 1989, **9**, 291–324; (*c*) G. P. Young, *Ann. Emerg. Med.*, 1984, **13**, 712–722.

10 (*a*) S. Chuanwen, C. Yanxia, L. Tianyan, W. Ying, F. Ting, W. Jing and X. Jiahua, *Chin. J. Chem.*, 2012, **30**, 1415–1422; (*b*) W. Zhang, X. Yang, W. Chen, X. Xu, L. Li, H. Zhai and Z. Li, *J. Agric. Food Chem.*, 2010, **58**, 2741–2745; (*c*) S. Lu, X. Shao, Z. Li, Z. Xu, S. Zhao, Y. Wu and X. Xu, *J. Agric. Food Chem.*, 2012, **60**, 322–330; (*d*) Z. Ye, L. Shi, X. Shao, X. Xu, Z. Xu and Z. Li, *J. Agric. Food Chem.*, 2013, **61**, 312–319.

11 (*a*) S. G. Ouellet, A. M. Walji and D. W. C. Macmillan, *Acc. Chem. Res.*, 2007, **40**, 1327–1339; (*b*) S. Hoffmann, M. Nicoletti and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13074–13075; (*c*) G. Li and J. C. Antilla, *Org. Lett.*, 2009, **11**, 1075–1078; (*d*) R. He, P. H. Toy and Y. Lama, *Adv. Synth. Catal.*, 2008, **350**, 54–60.

12 (*a*) A. B. Charette, S. Mathieu and J. Martel, *Org. Lett.*, 2005, **7**, 5401–5404; (*b*) L. Z. Chai, Y. K. Zhao, Q. J. Sheng and

Z.-Q. Liu, *Tetrahedron Lett.*, 2006, **47**, 9283–9285; (*c*) J. Chen and A. J. McNeil, *J. Am. Chem. Soc.*, 2008, **130**, 16496–16497; (*d*) R. Lavilla, M. C. Bernabeu, I. Carranco and J. L. Diaz, *Org. Lett.*, 2003, **5**, 717–720; (*e*) I. Carranco, J. L. Diaz, O. Jimenez, M. Vendrell, F. Albericio, M. Royo and R. Lavilla, *J. Comb. Chem.*, 2005, **7**, 33–41; (*f*) E. Vicente-Garcia, F. Catti, R. Ramon and R. Lavilla, *Org. Lett.*, 2010, **12**, 860–863; (*g*) S. Maiti, V. Sridharan and J. C. Menéndez, *J. Comb. Chem.*, 2010, **12**, 713–722.

13 (*a*) J.-P. Wan and Y. Liu, *RSC Adv.*, 2012, **2**, 9763–9777; (*b*) S. Ghosh, F. Saikh, J. Das and A. K. Pramanik, *Tetrahedron Lett.*, 2013, **54**, 58–62; (*c*) S. S. Kahandal, S. R. Kale, M. B. Gawande and R. V. Jayaram, *Catal. Sci. Technol.*, 2014, **4**, 672–680; (*d*) T. D. Ananda Kumar, P. Mohana, C. V. S. Subrahmanyam and K. Satyanarayana, *Synth. Commun.*, 2014, **44**, 574–582; (*e*) M. Nasr-Esfahani, S. J. Hoseini, M. Montazerozohori, R. Mehrabi and H. Nasrabadi, *J. Mol. Catal. A: Chem.*, 2014, **382**, 99–105; (*f*) C. G. Evans and J. E. Gestwicki, *Org. Lett.*, 2009, **11**, 2957–2959.

14 (*a*) H. S. P. Rao and K. Geetha, *Tetrahedron Lett.*, 2009, **50**, 3836–3839; (*b*) H. S. P. Rao, K. Geetha and M. Kamalraj, *RSC Adv.*, 2011, **1**, 1050–1059; (*c*) H. S. P. Rao, K. Geetha and M. Kamalraj, *Tetrahedron*, 2011, **67**, 8146–8154; (*d*) A. Parthiban, J. Muthukumaran, A. Moushumi Priya, S. Jayachandran, R. Krishna and H. S. P. Rao, *Med. Chem. Res.*, 2013, **23**, 642–659.

15 (*a*) P. Metzner and A. Thuillier, in *Sulfur Reagents in Organic Synthesis*, Academic Press, New York, 1994; (*b*) M. Kolb, *Synthesis*, 1990, 171–190; (*c*) Y. Tominaga and Y. Matsuda, *J. Heterocycl. Chem.*, 1985, **22**, 937–949; (*d*) H. Ila, H. Junjappa and P. K. Mohanta, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and T. L. Gilchrist, Pergamon Press, Oxford, 2001, vol. 13, pp. 1–24.

16 Y. Nakaike, N. Nishiwaki, M. Ariga and Y. Tobe, *J. Org. Chem.*, 2014, **79**, 2163–2169.

17 (*a*) S. E. Denmark and J. A. Sternberg, *J. Am. Chem. Soc.*, 1986, **108**, 8277–8279; (*b*) L. F. Tietze and A. Schuffenhauer, *Eur. J. Org. Chem.*, 1998, 1629–1637; (*c*) D. Cheng, J. Zhou, E. Saiah and G. Beaton, *Org. Lett.*, 2002, **4**, 4411–4414.

18 C. F. Bernasconi and Z. Rappoport, *Acc. Chem. Res.*, 2009, **42**, 993–1003.

19 J. Peter and N. Ralf, *Pestic. Sci.*, 2008, **64**, 1084–1098.

20 Y. Kashiwada, *Agrochem. Jpn.*, 1996, **68**, 18–19.

21 T. Iwasa, N. Motoyama, J. T. Ambrose and M. R. Roe, *Crop Prot.*, 2004, **23**, 371–378.

22 (*a*) A. Elbert and R. Nauen, *Pest Manage. Sci.*, 2000, **56**, 60–64; (*b*) K. D. Ninsin, *Pest Manage. Sci.*, 2004, **60**, 839–841; (*c*) D. M. Sanchez, R. M. Hollingworth, E. J. Grafius and D. D. Moyer, *Pest Manage. Sci.*, 2006, **62**, 30–37; (*d*) K. G. Gorman, G. Devine, J. Bennison, P. Coussons, N. Punchard and I. Denholm, *Pest Manage. Sci.*, 2007, **63**, 555–558.

23 S. Chuanwen, C. Yanxia, L. Tianyan, W. Ying, F. Ting, W. Jing and X. Jiahua, *Chin. J. Chem.*, 2012, **30**, 1415–1422.

