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An expedient four-component domino protocol for the regioselective synthesis of highly functionalized pyranopyrazoles and chromenopyrazoles via nitroketene-*N*,*S*-acetal chemistry under solvent-free condition

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ABSTRACT

Combinatorial library of pyranopyrazoles and chromenopyrazoles was regioselectively synthesized in excellent yield from ethylacetoacetate, hydrazinehydrate, substituted aldehyde/salicylaldehyde with nitroketene-*N*,*S*-acetal in the presence of piperidine under solvent-free condition (SFC) in an eco-benign manner. This novel strategy excludes tedious extraction, chromatographic separation and recrystallization processes. The final product could be obtained by simple filtration by the addition of ethanol to the reaction mixture. This domino protocol generates biologically significant heterocycles with the formation of C—C, C=C, C—N, C=N, C—O bonds and one stereo-centre in a single operation via condensation/Knoevenagel/Michael/annulation sequences.

In the modern drug development concern, synthesis of simple and complex bioactive heterocycles in a vast diversity with a single or minimum number of chemical routes is highly desirable. Multicomponent reactions (MCR)[1–3] have gained a noteworthy eminence as a synthetic tool for producing simple and structurally complex molecular entities with captivating biological features through the establishment and cleavage of numerous carbon–carbon and carbon-heteroatom bonds with the single operation under mild reaction condition, lesser reaction times, cost and man power and minimal waste by one pot reaction technique in both academics and industries. Due to ecological anxieties, the modern synthetic organic chemists pay much attention on synthetic pathways towards greener approaches to reduce drastic prerequisites for the reactions. Owing to the harmful effects of organic solvents on the environment and humans, solvent-free reactions have become a powerful tool in organic synthesis for delivering a huge number of biologically important heterocycles in greener approaches. Furthermore, solvent-free reactions offer several advantages such as faster reaction rate, reduced reaction time, less energy consumption, easy separation, and products with high yields and purity.[4] Diversity Oriented Synthesis (DOS) employed to generate library of novel compounds provides skeletally diverse simple and complex scaffolds generating multiple bonds and stereo-centres in single operation by integrating the Single Reactant Replacement (SRR)[5] strategy with MCR in greener approach.

Pyrazole is an indispensable heterocycle analogue which plays a vital role in many pharmaceutical and agrochemical industries. Especially these analogues find application in a broad variety of therapeutic areas, which include antimicrobials, analgesics, anti-inflammatory agents, CNS and oncology drugs.[6] Particularly some of the leading commercial drugs based on the pyrazole scaffold include celecoxib,[7] lonazolac[8] and rimonabant.[9] In recent days, pyrazole based analogues are constantly utilized as building blocks in drug discovery and development programs,[10] and are also found as key constituents of ligands for transition metals,[11] receptors in supramolecular chemistry,[12] liquid crystals[13] and polymers.[14] For these reasons, the innovation of novel approaches for the synthesis of polysubstituted pyrazole analogues is an important dynamic research area of high impact in fine chemistry.[15] Usually, the manifestation of two or more different heterocyclic moieties in a single molecule often enhances the biological profile remarkably. This encouraged us to focus on Target Oriented Syntheses (TOS)

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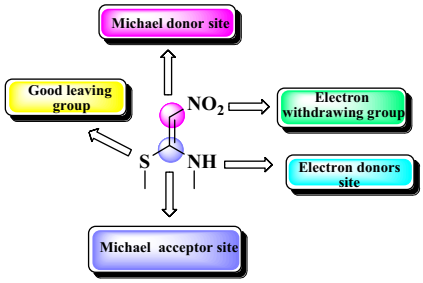


Figure 1. The special reactive profile of NMSM.

to design new heterocyclic compounds and develop novel a methodology for the regioselective synthesis of pyrazole fused pyrans and pyrazole substituted chromenes.

Pyranopyrazoles are fused heterocyclic compounds that deliver a huge number of pharmacological activities such as, bactericidal,[16] fungicidal,[17] insecticidal,[18] molluscicidal,[19,20] analgesic,[21] anti-inflammatory activities[22] and some of their analogues act as vasodilators, hypotensive,[23] hypoglycaemic and anticancer agents.[24,25] Similarly, chromene moiety broadly appears as an important structural motif in biologically active and natural products. It is broadly present in natural alkaloids, flavonoids, tocopherols and anthocyanins.[26] In addition, modern year's chromenes occupy more space in synthetic organic chemistry due to their vast utilities in medicinal chemistry.[27] Especially 2-amino-4*H*-chromenes are used as privileged medicinal scaffolds for the generation of small-molecule ligands with highly pronounced spasmolytic, diuretic, anticoagulant and antianaphylactic activities.[28]

The very first reported pyranopyrazole was synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene.[29] Several methods for the synthesis of pyranopyrazoles and chromene pyrazole derivatives have been reported in the past decades.[30] Recently, synthesis of pyranopyrazoles and chromenopyrazoles derivatives has been reported via a multicomponent approach using hydrazine with limited substrate scope.[31] Therefore, explorations of more general, efficient, rapid and viable routes are highly desirable.

This novel strategy to introduce an ambiphilic synthon which holds both nucleophilic and electrophilic sites has great potential for the development of pyranopyrazole and chromenopyrazoles in an effective manner. (*E*)-*N*-Methyl-1-(methylthio)-2-nitroethenamine (NMSM) is one such versatile synthon,[32] which contains four active sites with three functional groups on an ethene motif (Fig. 1) which was widely employed in the synthesis of several pharmacological important heterocycles such as ranitidine[33] and nizatidine[34] used for antiulcer drugs. Based on these key features, herein we demonstrate the use of the special reactivity of NMSM, for convenient combinatorial synthesis of pyranopyrazoles and chromenopyrazoles.

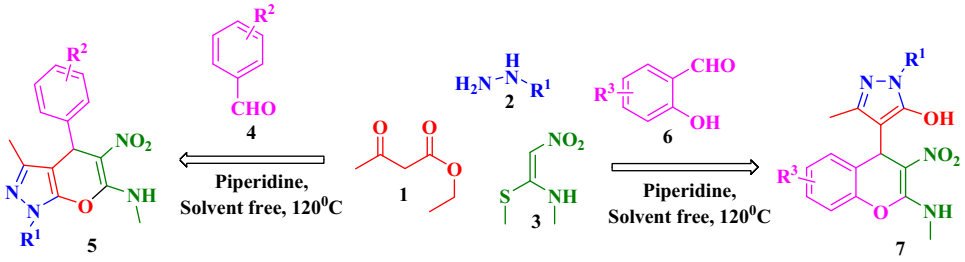
As part of our effort to develop biological potential small molecules by a new synthetic method,[35,36] a detailed literature survey by us revealed that there is no report on the use of piperidine as a catalyst in the synthesis of pyranopyrazoles and pyranochromenes derivatives utilizing NMSM under solvent-free conditions. Herein, we disclose a hitherto unreported facile chemo and regioselective four-component reaction for the combinatorial synthesis of novel highly functionalized pyranopyrazoles and chromenopyrazoles frameworks from ethylacetoacetate, hydrazinehydrate, substituted aldehydes/salicylaldehydes with the NMSN under solvent-free conditions at 120 °C in the presence of piperidine (Scheme 1). The reactions were completed within 0.5–3 h and the pure products were isolated in high yields simply by the addition of ethanol to the reaction mixture followed by filtration. The synthetic route is facile, convergent and allows easy placement of a variety of substituents around the periphery of the heterocyclic ring system.

The synthesis of 3-methyl-4-aryl-5-nitro-6- methylaminopyranopyrazoles **5** was first undertaken. A four- component reaction between ethylacetoacetate(1.0 mmol), hydrazinehydrate (1.0 mmol), 4-methylbenzaldehyde (1.0 mmol) and NMSM (1.0 mmol) was selected to optimize the reaction conditions. Initially, the above four-component coupling reaction was performed with an equimolar mixture in EtOH at room temperature without any catalyst. No product formation was observed even after 24 h of stirring.

Next we performed the reaction at thermal condition with various solvents like EtOH, MeOH, CH_3CN and different catalysts viz. Et_3N, piperidine, L-proline and the results are summarized in Table 1. All the catalysts promoted the reaction, albeit in low efficiency.

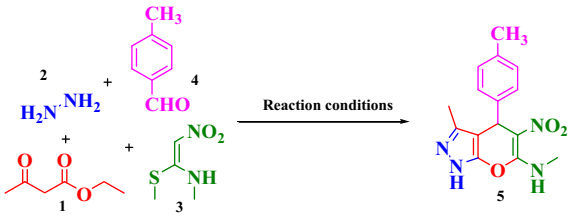
Next we performed the reaction under solvent-free condition and to our delight, the reaction was completed quickly providing good yields of the desired product. The main notable observation is that the product was obtained in 76% yield when piperidine was used as catalyst. With better results in hand, next we optimized the catalytic loading and found that by increasing the catalytic amount from 0.1 to 0.25 equiv we obtained better yield. Further by increasing the amount of catalyst, there was no improvement of yield. The efficiency of reaction was also evaluated with varying temperatures. Better results were obtained at 120 °C, while increasing the temperature to 150 °C, resulted in reduced yield due to decomposition of the product. Thus, the best yield was achieved employing 0.25 equiv of piperidine under solvent-free condition at 120 °C (Table 1, entries 19).

With the optimized conditions at hand, the scope and generality of this protocol were next examined by employing *N*-phenyl hydrazine and various aromatic aldehydes. A remarkably wide array of aromatic aldehydes were well tolerated. No obvious electronic effects of the aldehyde were observed, and the products were obtained in high yields (Table 2).[37] The formation of phenylpyrazolones needs a higher temperature for maximum yield in



Scheme 1. Synthesis of pyranopyrazoles **5** and chromenopyrazoles **7**.

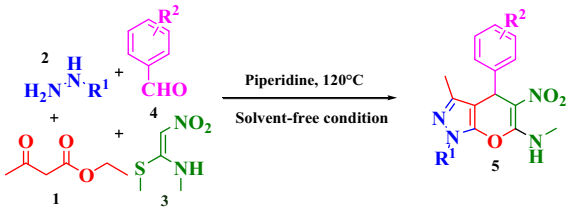
Table 1
Optimization of the reaction condition for the synthesis of pyranopyrazole[a] **5a**



Entry	Reaction condition	Time (h)	Yield[b] (%)
1	No catalyst, EtOH, rt	24	—[c]
2	No catalyst, EtOH, reflux	8	—[c]
3	Piperidine (0.1 equiv), EtOH, rt	24	—[c]
4	Piperidine (0.1 equiv), EtOH, reflux	5	65
5	Piperidine (0.25 equiv), EtOH, reflux	4.5	68
6	Piperidine (0.5 equiv), EtOH, reflux	6	68
7	Piperidine (0.5 equiv), MeOH, reflux	8	61
8	Piperidine (0.5 equiv), CH_3CN, reflux	6	58
9	Piperidine (0.5 equiv), toluene, reflux	8	10
10	TEA (0.25 equiv), EtOH, reflux	12	55
11	TEA (1.0 equiv), EtOH, reflux	8	58
12	L-Proline (0.25 equiv), EtOH, reflux	12	65
13	L-Proline (1.0 equiv), EtOH, reflux	8	65
14	DABCO (0.25 equiv), EtOH, reflux	6	57
15	DABCO (1.0 equiv), EtOH, reflux	8	61
16	No catalyst, solvent free	12	—[c]
17	Piperidine (0.1 equiv), solvent free, 80 °C	2	76
18	Piperidine (0.25 equiv), solvent free, 100 °C	1.5	81
19	Piperidine (0. 25 equiv), solvent free, 120 °C	0.5	86
20	Piperidine (0. 25 equiv), solvent free, 150 °C	0.5	81
21	Piperidine (1.0 equiv), solvent free, 120 °C	0.5	86
22	TEA (1.0 equiv), solvent free, 120 °C	2.5	76
23	DABCO (1.0 equiv), solvent free, 120 °C	2	73
24	L-Proline (1.0 equiv), solvent free, 120 °C	4	77
25	Pyrrolidine (1.0 equiv) solvent free, 120 °C	5	75
26	Morpholine (1.0 equiv) solvent free, 120 °C	6	72

[a] The reaction of ethylacetoacetate (1.0 mmol), hydrazine (1.0 mmol), 4-methylbenzaldehyde (1.0 mmol), NMSM (1.0 mmol).
[b] Isolated yield.
[c] No product obtained.

Table 2
Synthesis of pyranopyrazoles[a]



Entry	Compd	R^1	R^2	Time (h)	Yield (%)[b]
1	**5a**	H	4-Me	0.5	86
2	**5b**	H	4-NO_2	0.5	81
3	**5c**	H	4-OMe	1.0	82
4	**5d**	H	2-F	0.5	85
5	**5e**	H	4-Cl	0.75	82
6	**5f**	H	C_4H_4	1.0	79
7	**5g**	H	2,4-Cl	0.75	76
8	**5h**	H	4-F	0.5	83
9	**5i**	H	4-Br	0.5	86
10	**5j**	C_6H_5	4-Br	2.5	83
11	**5k**	H	2-NO_2	0.5	78
12	**5l**	C_6H_5	2-NO_2	2.25	81
13	**5m**	C_6H_5	3-NO_2	2.5	80
14	**5n**	C_6H_5	4-OMe	3.0	78
15	**5o**	C_6H_5	4-F	2.5	82
16	**5p**	C_6H_5	2-F	2.25	78
17	**5q**	C_6H_5	2-Me	2.75	77
18	**5r**	C_6H_5	C_4H_4	3.0	76
19	**5s**	H	2-Me	1.5	79

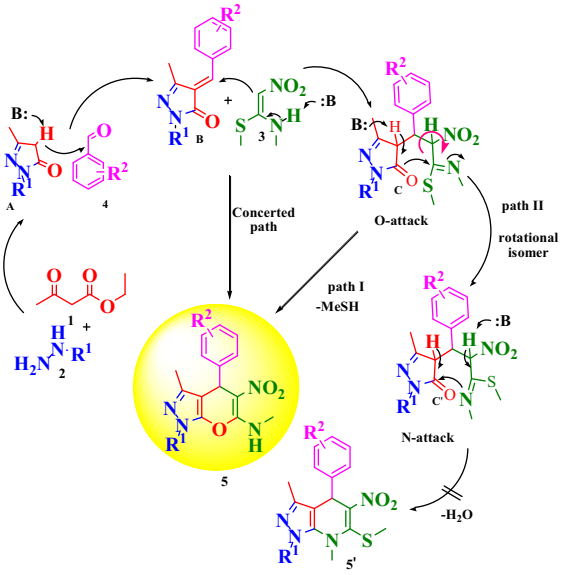
[a] Reaction performed at 120 °C under SFC.
[b] Isolated yield.

solvent-free condition. The key point makes this methodology suitable for vast structural diversity.

Taking into consideration the entire outcome, a plausible mechanistic pathway for the domino reaction is depicted in Scheme 2. The first step is condensation of ethylacetoacetate **1** with hydrazinehydrate **2** to give pyrazolone **A**. The intermediate **A** undergoes Knoevenagel reaction with aldehyde **4** to give Michael acceptor **B**. The adduct **B** immediately undergoes Michael-type addition with nitoketene-*N*,*S*-acetal (NMSM) **3** to generate the open chain intermediate **C**. The intermediate **C** undergoes intramolecular *O*-cyclization via path **I** to give compound **5** with the elimination of MeSH. The intermediate **C** may exist in another rotameric form **C′**, which could probably undergo N-cyclizations via path **II** to give compounds **5′**. During our investigation, we did not perceive even traces of **5′**, and only **5** was obtained exclusively, suggesting *O*-cyclization through the route **I**, making the protocol highly chemo- and regioselective.

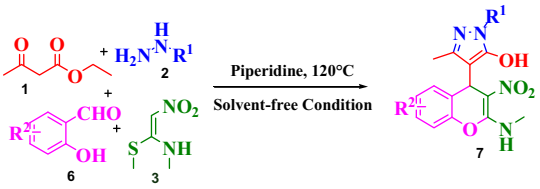
After successful coupling of NMSM with ethylacetoacetate, hydrazines and various aromatic aldehydes under solvent-free conditions, salicylaldehyde was utilized in place of aromatic aldehydes in order to gain further understanding about this transformation, and to show the versatility of this protocol. Consequently, reaction of **1, 2**and **6** with nitroketene-*N*,*S*-acetal provided easy access to chromenopyrazoles **7** in good yields (Table 3). The capacity of the reaction was fruitfully proved for a wide range of salicylaldehydes and phenyl hydrazines.

A plausible mechanistic pathway for chromenopyrazoles is depicted in Scheme 3. The first step is condensation of ethylacetoacetate **1** with hydrazinehydrate **2** to give pyrazolone **A**. The intermediate **A** undergoes Knoevenagel reaction with salicylaldehyde **6** to give Michael acceptor **B**. The adduct **B** immediately undergoes Michael-type addition with nitoketene-*N*,*S*acetal (NMSM) **3** to generate the open chain intermediate **C**. The intermediate **C** undergoes intramolecular phenolic *O*-cyclization via path **I** to give compound **7** with elimination of MeSH. The intermediate **C** may exist in its two rotameric forms **C′** and **C″**, which could probably undergo enolic *O*- or *N*-cyclizations via path **II** or **III** to give



Scheme 2. Plausible reaction scenario for the formation of **5**.

Table 3
Synthesis of chromenopyrazoles[a]



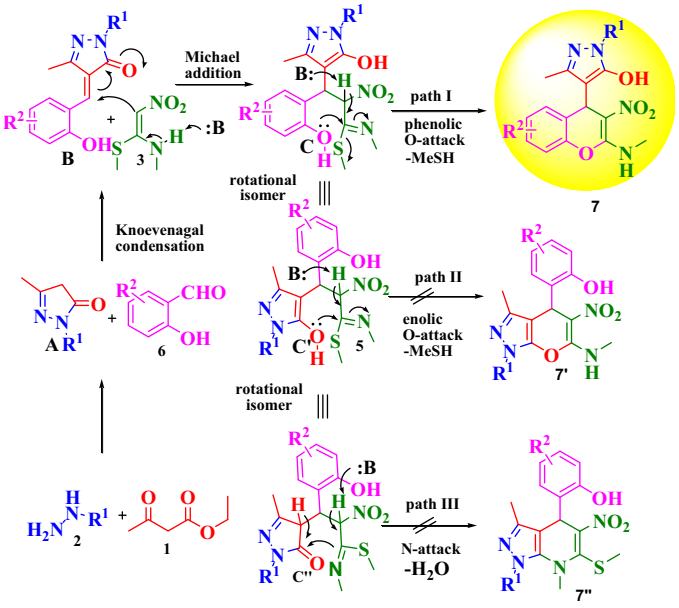
Entry	Compd	R^1	R^2	Time (h)	Yield[b] (%)
1	**7a**	H	H	1.0	79
2	**7b**	H	5-Br	0.75	81
3	**7c**	H	5-Cl	0.75	80
4	**7d**	C_6H_5	H	3.0	82
5	**7e**	C_6H_5	3,5-Br	2.25	84
6	**7f**	C_6H_5	5-NO2	2.20	81
7	**7g**	C_6H_5	4-OMe	2.5	77
8	**7h**	H	3-OEt	1.5	74
9	**7i**	H	3,5-Br	1.0	83

[a] Reaction performed at 120 °C under SFC.
[b] Isolated yield.

compounds **7′** and **7″**, respectively. During our investigation, we did not observe even traces of **7′** or **7″**, and 7 was obtained exclusively, suggesting phenolic O-cyclization through the route **I** was more facile in simple greener approach.

The main advantage of this domino protocol is the simple work-up, and the product is obtained in high purity simply by trituration with ethanol, which makes this methodology facile, practical and rapid to perform. The purity of the product was enough for spectroscopic analysis without any further purification. The structures of all the newly synthesized compounds **5** and **7** were well characterized from their satisfactory spectral (IR, ^1H, ^{13}C NMR, and Mass) data. The mass spectra of the synthesized compounds displayed molecular ion peaks at the appropriate *m*/*z* values. Further the structure was explicitly established by the single crystal X-ray diffraction analysis of compound **5a** (Fig. 2).[38]

In summary, we have developed a convenient, efficient, chemoselective and regioselective synthesis of pyranopyrazoles and



Scheme 3. Plausible reaction scenario for the formation of **7**.

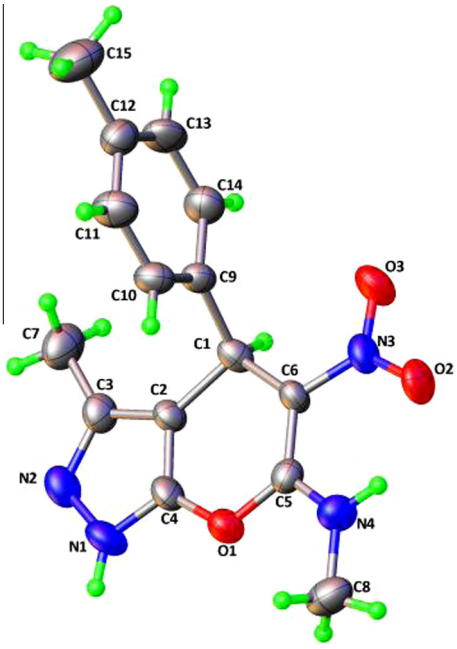


Figure 2. ORTEP diagram of **5a**.

chromenopyrazoles frameworks by the reaction of ethylacetoacetate, hydrazines, aromatic aldehydes/salicylaldehydes and nitroketene-*N*,*S*-acetal in the presence of piperidine under solvent-free conditions. Simple, novel and regioselective synthesis with the formation of C—C, C=C, C—N, C=N and C—O bonds with one stereocenter in a single operation with efficient utilization of all the reactants has been accomplished in our approach. The salient feature of this methodology is short reaction time, excellent yield, low-cost, operational simplicity, vast structural diversity and more importantly the purification of compounds by a non-chromatography method to make this process very significant for academic research and practical applications in greener approach. Moreover, the secondary amine and nitro substituents in the 2- and 3-positions of the compounds **5** and **7** are reactive entities, making these compounds good candidates as precursors for further synthetic transformations for various useful purposes. Further studies on the extension of the scope of the use NMSM in synthetic applications are currently under way in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.019.

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37. *General procedure for the synthesis of **5** and **7***: A dried 10 mL round bottom flask was charged with ethylacetoacetate (1.0 mmol), hydrazine (1.0 mmol), substituted aldehydes/salicylaldehydes (1.0 mmol), nitroketene-*N*,*S*-acetal (NMSM) (1.0 mmol) and piperidine (0.25 mmol), was added to the reaction mixture and heated in an oil bath at 120 °C for the stipulated period of time. After completion of the reaction (monitored by TLC) ethanol (2 mL) was added to the reaction mixture. The products appeared as a solid, by trituration with ethanol, was filtered and washed with another 2 mL of EtOH to remove the base and other impurities. Finally, the products **5** and **7** was dried and were pure enough for the spectral investigations.
Spectral data of pyranopyrazole **5a**
White solid; mp 234–236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (s, 3H, Me), 2.23 (s, 3H, Me), 3.15 (d, J = 4.2 Hz, 3H, NMe), 5.13 (s, 1H, CH), 7.05 (d, J = 8.1 Hz, 2H, ArH), 7.09 (d, J = 8.2 Hz, 2H, ArH), 10.64 (s, 1H, NH), 12.29 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6) δ 10.2, 21.1, 28.7, 37.3, 99.7, 109.5, 127.6, 129.1, 135.7, 136.5, 141.5, 153.6, 160.3. IR (KBr, cm^{-1}): 3218, 1638, 1604, 1535, 1467, 1361, 1213, 1161, 1058, 804, 553, 467. ESI-Mass m/z: 299 (M$^+$−1).
Spectral data of chromenopyrazole **7a**
Pale yellow solid; mp 258–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H, Me), 3.14 (d, J = 5.0 Hz, 3H, NMe), 5.12 (s, 1H, CH), 7.08–7.31 (m, 4H, ArH), 9.33 (s, 1H, NH), 10.39 (q, J = 4.6 Hz, 1H, NH), 11.08 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.3, 28.4, 30.6, 104.2, 106.9, 116.2, 125.2, 125.6, 128.1, 129.8, 136.9, 148.0, 159.6. IR (KBr, cm^{-1}): 8298, 1609, 1644, 1609, 1580, 1480, 1373, 1215, 1174, 762, 667, 473. ESI-Mass m/z: 303 (M$^+$+1).
38. Crystallographic data for the compound **5a** in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 957327. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].