



Tandem Knoevenagel-[3+2] cycloaddition-elimination reactions: one-pot synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles

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ABSTRACT

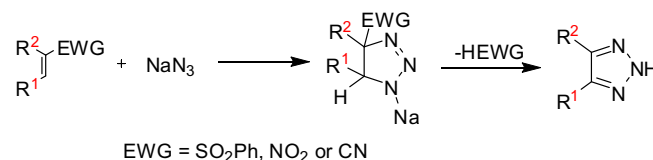
Sodium azide has been found to catalyse Knoevenagel condensation between aromatic aldehyde and cyano compound with active methylene hydrogens and this has led to a successful route for the one pot synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles from aldehydes through Knoevenagel-[3+2]cycloaddition-elimination sequence. In the formation of 5-aryl-2H-1,2,3-triazole-4-carbonitrile derivatives, the reaction has been found to occur efficiently in water.

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1,2,3-Triazole is the core moiety in several therapeutic agents, including antifungal,¹ antiallergic,² anti-viral,³ HIV-1 inhibitors,⁴ antimicrobial agents⁵ and selective β_3 -adrenergic receptor agonists.⁶ 4,5-Disubstituted 1,2,3-(NH)-triazoles have been found application as anti-inflammatory agents,⁷ neurokinin-1 receptor antagonists⁸ and also the inhibitors of VIM-2 metallo- β -lactamase.⁹ 5-Aryl-2H-1,2,3-triazole-4-carbonitrile derivatives are HER2 tyrosine kinase inhibitors¹⁰ and used for optical brighteners for lacquers, natural or synthetic fibres and films.¹¹ Because of these extensive applications, new cost effective greener methods for the preparation of this class of compounds are worth investigating.

The recent discovery of copper and ruthenium catalysed azide-alkyne 1,3-dipolar addition reactions is efficient protocols for the synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles, respectively,^{12,13} but are inconvenient to prepare 4,5-disubstituted 1,2,3-(NH)-triazoles. Only a few methods are available for the synthesis of 4,5-disubstituted 1,2,3-(NH)-triazole,¹⁴ the main one being [3+2] cycloaddition reaction of sodium azide with electron deficient olefin followed by elimination (Scheme 1). In such reactions, the ease of elimination of the groups is found to be in the order of benzenesulphonyl > nitro > cyano.¹⁵ These reactions require harsh conditions and also lead to unsatisfactory yield,¹⁶ though this methodology has been applied for different types of electron deficient alkenes.^{14b,17}

In many of these reactions, the eliminating group has been either benzenesulphonyl or nitro but the elimination of cyano



Scheme 1. Cycloaddition/elimination method for the synthesis of substituted (NH)-triazoles.

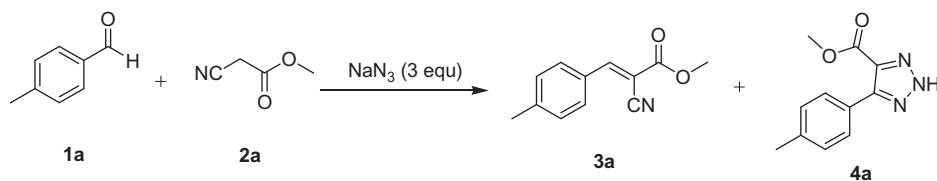
group has not yet explored. In the present work, a detailed investigation has been undertaken in order to improve the scope of this reaction under one-pot process and to find out a greener route to this class of compounds and the interesting results obtained, including the serendipity finding of azide as an efficient catalyst for Knoevenagel condensation, are reported in this article.

In an attempt to prepare the target 4,5-disubstituted 1,2,3-(NH)-triazole in a multicomponent one-pot fashion, *p*-tolualdehyde (**1a**) and methyl cyanoacetate (**2a**) was allowed to react with sodium azide in the presence of piperidine. Only the Knoevenagel product (**3a**) was obtained with a trace amount of expected triazole (**4a**), even at 80 °C (Table 1, entries 1 and 2). L-Proline has also been used for this reaction, but only 5–10% of the triazole (**4a**) was obtained (Table 1, entries 3 and 4). Obviously, the Knoevenagel product obtained (**3a**) is reluctant to undergo [3+2] cycloaddition reaction with sodium azide under these conditions. In order to effect the cycloaddition in a single step, several catalysts were tried to increase the reactivity of sodium azide. In one such reaction, lithium chloride, which can form more reactive lithium azide,

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Table 1
Optimisation of the conditions for the three component reaction



Entry	Reagent (equiv)	Solvent	T (°C)	Time (h)	Yield (%) ^a	
					3a	4a
1	Piperidine (0.2)	DMSO	30	24	95	Trace
2	Piperidine (0.2)	DMSO	80	24	95	Trace
3	L-proline (0.2)	DMSO	30	24	92	5
4	L-proline (0.2)	DMSO	80	24	85	10
5	LiCl (3.2)	DMF	30	24	83	10
6	LiCl (3.2)	DMF	70	24	70	20
7	None	DMF	30	2	98	Trace
8	Et ₃ N.HCl (2.5)	DMSO	70	8	0	55
9	Et ₃ N.HCl (2.5)	DMF	70	10	0	65
10	Et ₃ N.HCl (2.5)	H ₂ O	100	24	80	Trace
11	Et ₃ N.HCl (1.5)	DMF	70	15	20	50 ^b

^a Isolated yield.

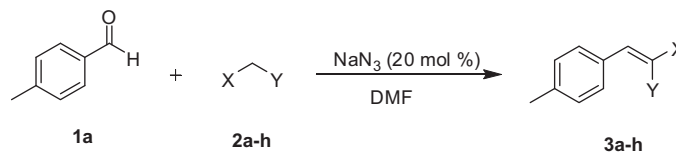
^b Two equivalent of NaN₃ used.

was employed but no significant improvement in the yield of **4a** has been noticed, though a marginal rise has been observed (Table 1, entries 5 and 6). During these trials, the reaction of *p*-tolualdehyde, methyl cyanoacetate and sodium azide without any catalyst has also been attempted and only a trace amount of **4a** was formed. But surprisingly, Knoevenagel product (**3a**) was formed in 98% (Table 1, entry 7). Thus, it is realized that azide has catalysed Knoevenagel reaction to near perfection without any base. When the three component reaction was carried out in the presence of triethylammonium chloride (Et₃N.HCl), which was found to enhance the reactivity of sodium azide in a different context,¹⁸ the reaction has gone smoothly yielding 65% of **4a** (Table 1, entry 9). It is clear that Et₃N.HCl promotes the cycloaddition reaction by activating sodium azide. The fact that Et₃N.HCl does not catalyse the Knoevenagel condensation has been confirmed by a separate experiment.¹⁹ The results of the optimisation of the reaction with different catalysts and solvents are provided in Table 1.

Though numerous reagents have been reported to catalyse Knoevenagel condensation,²⁰ which is the best carbon-carbon bond making reaction, this is the first time that sodium azide has been found to catalyse this reaction. To test the efficacy of sodium azide in Knoevenagel condensation, numbers of active methylene compounds were allowed to react with *p*-tolualdehyde in the presence of sodium azide and the results are presented in Table 2. Interestingly, it can be seen that azide catalysed Knoevenagel condensation is successful only when the active methylene compound contains at least one cyano group as the activating group (Table 2, products **3a**, **3c**, **3f** and **3h**). This reaction has led to *E*-isomer alone, which was confirmed by the comparison of their spectroscopic properties with those available in the literature for known products.²¹ It must be mentioned that in the case of aliphatic aldehydes, the Knoevenagel condensation is not proceeding smoothly under the described reaction conditions.

After establishing the role of sodium azide in the Knoevenagel reaction and that of Et₃N.HCl in [3+2] cycloaddition reaction, synthesis of several 4,5-disubstituted 1,2,3-(*NH*)-triazoles (**4b–4v**) has been carried out from a range of aromatic aldehydes (**1**, where Ar is substituted phenyl or heteroaryl) and cyano compounds with active methylene (**2**, where R is OCH₃, NH₂ or *N*-piperidyl) under optimized conditions (Table 3).^{22,23} The results demonstrate that

Table 2
Sodium azide catalysed Knoevenagel condensation



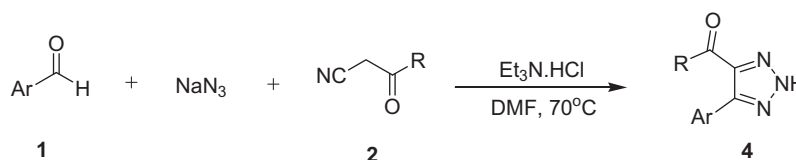
Product	X	Y	T (°C)	Time (h)	Yield (%) ^a
3a	COOCH ₃	CN	30	12	96
3a	COOCH ₃	CN	70	2	98
3a	COOCH ₃	CN	70	12	30 ^b
3b	COCH ₃	COCH ₃	70	16	0
3c	CN	CN	30	0.5	90
3d	COOCH ₂ CH ₃	C ₆ H ₅ CO	70	16	0
3e	COOCH ₃	COOCH ₃	70	16	0
3f	COOCH ₂ CH ₃	CN	70	2	92
3g	COOCH ₃	COCH ₃	70	16	0
3h	CONH ₂	CN	70	5	91

^a Isolated yield.

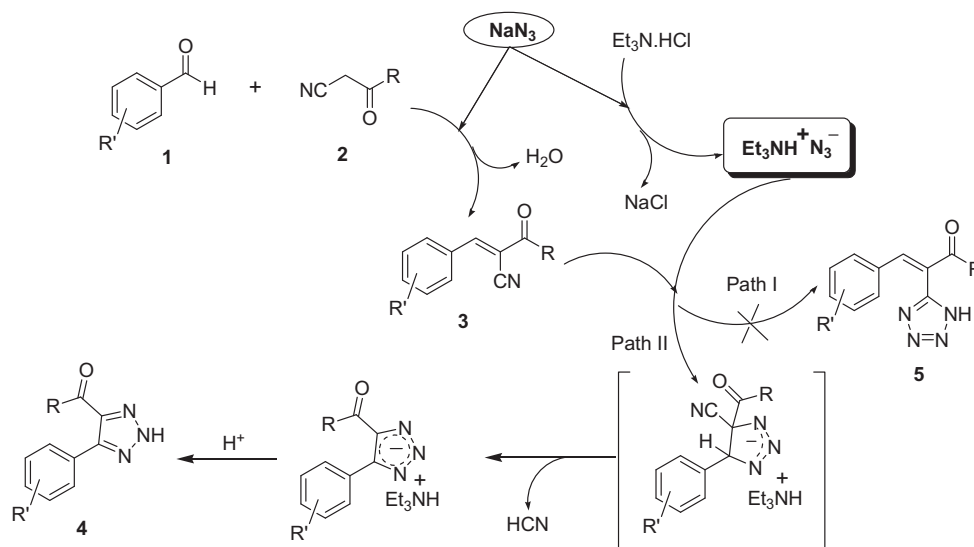
^b The reaction was carried out in the absence of NaN₃.

strong electron donating group (like methoxy) in the phenyl ring leads to comparatively less yield (**4j** and **4k**), whereas other groups such as SCH₃, CH₃, OPh and Cl do not affect the product yield (**4d–4h**). This reaction proceeded smoothly even in the presence of free carboxylic acid substituent in the phenyl ring without the need for protection (**4i**). It can be seen that cyanoacetamide involved reaction has resulted in good yield of the triazole derivatives (**4n–4u**) compared to those involving methyl cyanoacetate. The reported method by Lam and co-workers^{17a} yielded only 37 and 51% of **4o** and **4t** respectively, whereas our methodology resulted in 82 and 84% of these products by a relatively simple process. 1-(Cyanoacetyl)piperidine also works well in this reaction (**4v**).

On the basis of above results, a plausible mechanism for the formation of (*NH*)-triazoles (**4**) is proposed in Scheme 2. Path I leading to the formation of a tetrazole **5** via nitrile-azide cycloaddition has not taken place, indicating the product selectivity associated with this reaction.

Table 3Synthesis of 4,5-disubstituted (NH)-1,2,3-triazoles **4** (**4a–4v**)^a

Entry	Ar	R	Time (h)	Product	Yield ^b (%)
1	4-MeC ₆ H ₅	OCH ₃	10	4a	65
2	Ph	OCH ₃	7	4b	68
3	4-CH(CH ₃) ₂ C ₆ H ₅	OCH ₃	9	4c	70
4	3-OPhC ₆ H ₅	OCH ₃	8	4d	70
5	4-SMeC ₆ H ₅	OCH ₃	8	4e	72
6	2-ClC ₆ H ₅	OCH ₃	8	4f	53
7	4-ClC ₆ H ₅	OCH ₃	8	4g	78
8	3,4-Me ₂ C ₆ H ₄	OCH ₃	10	4h	62
9	3-COOHC ₆ H ₅	OCH ₃	6	4i	76
10	4-OCH ₃ C ₆ H ₅	OCH ₃	10	4j	51
11	3,4-(OMe) ₂ C ₆ H ₄	OCH ₃	12	4k	50
12	2-Thienyl	OCH ₃	8	4l	65
13	3-Thienyl	OCH ₃	8	4m	61
14	4-MeC ₆ H ₅	NH ₂	10	4n	78
15	Ph	NH ₂	10	4o	82
16	3-(OPh)C ₆ H ₅	NH ₂	10	4p	80
17	4-SMeC ₆ H ₅	NH ₂	10	4q	87
18	2-ClC ₆ H ₅	NH ₂	10	4r	72
19	4-ClC ₆ H ₅	NH ₂	10	4s	90
20	2-Thienyl	NH ₂	10	4t	84
21	3-Thienyl	NH ₂	10	4u	81
22	4-ClC ₆ H ₅	N-piperidyl	10	4v	70

^a Reactions and condition: 5 mmol of **1**, 5 mmol of **2**, 15 mmol of NaN₃, 12.5 mmol of Et₃N.HCl in 15 mL DMF, 70 °C, 6–10 h.^b Isolated yield.**Scheme 2.** Mechanism for the formation of **4**.

It can be seen that in the three-component reaction described in Table 3, XCH₂CN has been employed as one of the components and ultimately cyano group gets eliminated retaining X as the substituent in the triazole ring. We wanted the cyano group to be retained in the triazole ring in a multicomponent reaction of the above type and the identified component for such a reaction is phenylsulfonyl acetonitrile (**6**).²⁴

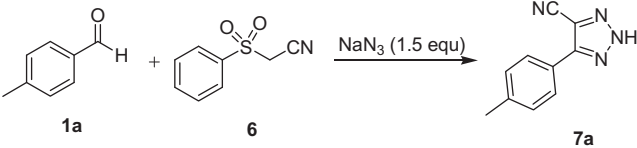
The three-component reaction of *p*-tolualdehyde (**1a**) and phenylsulfonyl acetonitrile (**6**) with sodium azide in DMF at 30 °C, resulted in 75% of **7a** after 15 h, but 90% of **7a** was obtained after 3 h at 70 °C (Table 4, entries 1 and 2). When the reaction was carried

out at 90 °C, it completed in 1 h (Table 4, entry 3). Interestingly this tandem Knoevenagel-cycloaddition-elimination reaction proceeded smoothly in aqueous medium and also giving excellent yield of the (NH) triazole **7a** (Table 4, entry 4). It can be noted that water is not a suitable medium for the formation of **4** (Table 1 entry 10).

To illustrate the generality of this reaction, a diverse set of **7** (Table 5 compounds **7b–7q**) was prepared (where Ar is substituted phenyl or heteroaryl).²⁵

In summary, it is shown that a diverse set of 4,5-disubstituted (NH)-1,2,3-triazole can be prepared efficiently by a Knoevenagel-cycloaddition-elimination reaction sequence from aromatic alde-

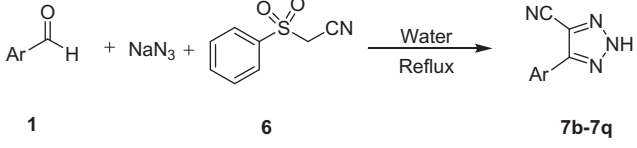
Table 4
Optimization of reaction condition for the formation of **7a**



Entry	Solvent	T (°C)	Time (h)	Yield of 7a (%) ^a
1	DMF	30	15	75
2	DMF	70	3	90
3	DMF	90	1	93
	Water	reflux	1	95

^a Yield of isolated product.

Table 5
Synthesis of 5-aryl-4-cyano-(NH)-1,2,3-triazole derivatives **7 (7b–7q)**



Product	1	Time (h)	Yield (%)
7b	Ar = Phenyl	1	91
7c	Ar = 4-Chlorophenyl	1	99
7d	Ar = 4-Methylthiophenyl	4	65
7e	Ar = 3-Phenoxyphenyl	3	99
7f	Ar = 3-Carboxyphenyl	1	96
7g	Ar = 2-Fluorophenyl	1	95
7h	Ar = 4-Methoxyphenyl	1	90
7i	Ar = 3-Methoxy-4-fluorophenyl	1	88
7j	Ar = 3,4,5-Trimethoxyphenyl	1	93
7k	Ar = 5-Acetoxyethyl-2-furyl	2	75
7l	Ar = 2-Thienyl	4	60
7m	Ar = 3-Thienyl	3	70
7n	Ar = 2-Thiazolyl	0.5	93
7o	Ar = 3-Pyridyl	1	84
7p	Ar = 4-Pyridyl	0.5	88
7q	Ar = 4-Quinoliny	1	76

hyde and active methylene compound where sodium azide not only acts as the reactant but also serves as the catalyst for Knoevenagel condensation. The generation of electron deficient alkene in a separate step is avoided in this protocol. It has also demonstrated that water can act as a good medium for this class of reactions. Simple reaction conditions, easy isolation process and good yields of the triazoles are the salient features of the methodology.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.146.

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- General procedure for the synthesis of Knoevenagel product **3a**, **3c**, **3f** and **3h**: A mixture of *p*-tolaldehyde (**1a**) (5 mmol), active methylene compound (**2**) (5 mmol) and sodium azide (20 mol %) was mixed with DMF (10 mL) in a round-bottomed flask. The reaction mixture was heated in an oil bath at given temperature for the desired time (Table 2). After cooling to room temperature, the reaction mixture was poured into cold water (100 mL), the solid obtained was collected by filtration and washed with water to afford pure **3** as a white solid. See Supplementary data for spectral data of all compounds.
- General procedure as exemplified for Methyl 5-*p*-tolyl-2H-1,2,3-triazole-4-carboxylate (**4a**): To a mixture of *p*-tolaldehyde (0.5 g, 4.2 mmol), methyl

- cyanoacetate (0.41 g, 4.2 mmol) and Et₃N·HCl (1.43 g, 10.4 mmol) in DMF (12 mL) was added sodium azide (0.81 g, 12.5 mmol). The mixture was then stirred at 70 °C for 10 h. Following, to the reaction mixture was added water (50 mL), 10% HCl solution (2 mL) at room temperature and extracted with ethyl acetate (2 × 75 mL). The combined organic phases were washed with water (3 × 100 mL), brine solution (1 × 100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was subjected to column chromatography with dichloromethane/methanol (99.5/0.5) as eluent to obtain the desired **4a** (0.585 g, 65% yield) as a white solid; mp 106–108 °C; *R*_f 0.45 (DCM/MeOH, 95:5); IR (KBr) 3138, 1721, 1528, 1483, 1451, 1204, 1149, 1119, 1055, 987 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 2.36 (s, 3H), 3.84 (s, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 9.85 (br s, 1H); δ_{C} (100 MHz, CDCl₃) 21.5, 52.4, 124.3, 129.1, 129.2, 133.7, 140.1, 145.7, 161.8; Anal. Calcd for C₁₁H₁₁N₃O₂: C, 60.82; H, 5.10; N, 19.34%. Found: C, 60.77; H, 5.08; N, 19.31; ESI-*m/z* calcd for [C₁₁H₁₁N₃O₂ – H]⁺ 216.1, found 216.1.
23. Spectroscopic data for representative example: 5-*p*-Tolyl-2H-1,2,3-triazole-4-carboxamide (**4n**, Table 3, entry 14) White solid; mp 244–245 °C; *R*_f 0.37 (DCM/MeOH, 95:5); IR (KBr) 3388, 3338, 3282, 3225, 1676, 1600, 1578, 1491, 1413, 1352, 1281, 1273, 1236, 1191 cm⁻¹; δ_{H} (400 MHz, DMSO-*d*₆) 2.35 (s, 3H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.50 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.86 (s, 1H), 15.5 (br s, 1H); δ_{C} (75 MHz, DMSO-*d*₆) 21.7, 129.5, 129.7, 138.2, 139.4, 163.8; Anal. Calcd for C₁₀H₁₀N₄O: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.36; H, 4.97; N, 27.68; ESI-*m/z* calcd for [C₁₀H₁₀N₄O – H]⁺ 201.1, found 201.1. (5-(4-Chlorophenyl)-2H-1,2,3-triazol-4-yl)(piperidin-1-yl)methanone (**4v**, Table 3, entry 22) White solid; mp 210–211 °C; *R*_f 0.46 (DCM/MeOH, 95:5); IR (KBr) 3073, 1592, 1529, 1501, 1446, 1368, 1284 cm⁻¹; δ_{H} (400 MHz, DMSO-*d*₆) 1.30–1.31 (m, 2H), 1.56–1.57 (m, 4H), 3.19–3.20 (m, 2H), 3.65–3.66 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 15.47 (br s, 1H); δ_{C} (75 MHz, DMSO-*d*₆) 24.7, 26.1, 26.9, 43.1, 48.3, 128.9, 129.3, 129.9, 134.3, 162.4; Anal. Calcd for C₁₄H₁₅ClN₄O: C, 57.83; H, 5.20; N, 19.27. Found: C, 57.79; H, 5.19; N, 19.24; ESI-*m/z* calcd for [C₁₄H₁₅ClN₄O – H]⁺ 289.1, found 289.1. See [Supplementary data](#) for spectral data of all other compounds.
24. (a) Rahimizadeh, M.; Rajabzadeh, G.; Khatami, S. M.; Eshghi, H.; Shiri, A. J. *Mol. Catal. A: Chem* **2010**, 323, 59–64; (b) Surya Prakash, G. K.; Zhao, X.; Chacko, S.; Wang, F.; Vaghoo, H.; Olah, G. A. *Beilstein J. Org. Chem.* **2008**, 4, 1–7; (c) Zhou, W.; Xu, L. Z. X.; Zhang, Z.; Xuebao, W. H. *Wuji Huaxue Xuebao* **1992**, 8, 88–90.
25. General procedure as exemplified for 5-*p*-Tolyl-2H-1,2,3-triazole-4-carbonitrile (**7a**). A mixture of *p*-tolualdehyde (0.5 g, 4.2 mmol), phenylsulfonyl acetonitrile **6** (0.75 g, 4.2 mmol) and sodium azide (0.4 g, 6.25 mmol) in water (15 mL) was stirred under reflux for 1 h. The resulting mixture was then cooled to 5 °C, the solid obtained was filtered and washed with water (50 mL) to afford pure **7a** (0.73 g, 95% yield) as a white crystals; mp 175–177 °C; *R*_f 0.38 (DCM/MeOH, 95:5); IR (KBr) 2873, 2240, 1613, 1510, 1275 cm⁻¹; δ_{H} (400 MHz, DMSO-*d*₆) 2.39 (s, 3H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 16.47 (br s, 1H); δ_{C} (100 MHz, CDCl₃) δ 21.0, 112.9, 116.3, 122.7, 126.4, 129.8, 140.8; Anal. Calcd for C₁₀H₈N₄: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.16; H, 4.30; N, 30.39; ESI-*m/z* calcd for [C₁₀H₈N₄ – H]⁺ 183.1, found 183.1. See [Supplementary data](#) for spectral data of all other compounds.