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Graphical Abstract

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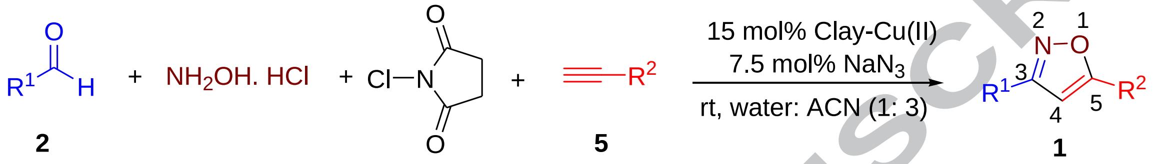

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Montmorillonite clay Cu(II) catalyzed domino one-pot multicomponent synthesis of 3,5-disubstituted isoxazoles

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ABSTRACT

A simple and efficient one-pot multicomponent approach for the synthesis of 3,5-disubstituted isoxazoles directly from corresponding aldehydes and terminal alkynes using recyclable montmorillonite clay supported Cu(II)/ NaN_3 catalytic system under aqueous conditions have been developed. The 'domino' one-pot MCR approach involves hydroxyamination of aldehydes followed by chlorination and then generation of reactive 'nitrile oxide' which undergoes 1,3-dipolar cycloaddition with alkynes to produce 3,5-disubstituted isoxazoles. The method is operationally simple, regioselective, economical and possesses excellent functional group compatibility to synthesize structurally diverse isoxazoles in good yields.

Isoxazoles are commonly encountered in variety of natural products and drugs and are known to exhibit diverse range of pharmacological activities.[1] Because of their medicinal importance, synthetically this scaffold has been extensively investigated.[2,3] The cycloaddition approach has been extensively used for the preparation of isoxazoles[3] and structurally related triazoles.[4] To access 3,5-disubstituted isoxazoles,[3] the 1,3-dipolar cycloaddition of nitrile oxides with alkynes is most direct and frequently used approach.[5] This method involves *in situ* generation of Cu(I) from Cu(II) using reducing agent like sodium ascorbate because Cu(I) is unstable; moreover in reported protocols excess base was employed for the generation of nitrile oxide. In general, the nitrile oxides react with terminal alkynes without catalyst, but this leads to formation of both isoxazole regioisomers. The significant formation of byproducts has been the major concern (particularly with reactive nitrile oxides) leading to poor yields and difficulty in product isolations. Furthermore, currently available protocols mostly involve the use of homogeneous catalytic systems. With the advent of green chemistry protocols, in recent years heterogeneous catalysts are becoming overwhelmingly important. Since isoxazole class of compounds are medicinally important, development of simple, efficient and economical protocol for their synthesis using recyclable catalyst will be of great use.

As a part of our work on development of tandem protocols[6,7] for the preparation of medicinally important scaffolds and in continuation to our recent work on synthesis of 1,2,3-triazoles,[7] herein we report one-pot multicomponent approach for the synthesis of 3,5-disubstituted isoxazoles **1** directly from aldehydes **2** and acetylenes **5** via cycloaddition reaction between *in situ* generated nitrile oxide and acetylenes (Figure 1).

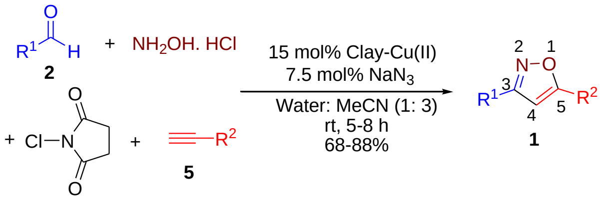

Figure 1. Clay-Cu(II)-catalyzed one-pot synthesis of 3,5-disubstituted isoxazoles

The hydroximyl chlorides **4** are the key precursors which are essential for *in situ* generation of reactive nitrile oxides which takes part in 1,3-dipolar cycloaddition reaction for the synthesis of 3,5-disubstituted isoxazoles. The precursor **4a** was synthesized from corresponding aldehyde **2a** using a two-step procedure as shown in Scheme 1.

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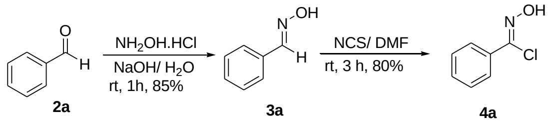
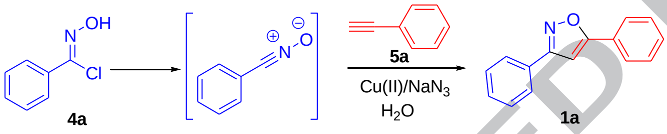


Scheme 1. Synthesis of hydroximyl chloride **4a** from aldehyde **2a**

After the synthesis of hydroximyl chloride **4a**, we explored the utility of clay-Cu(II)/NaN_3 catalytic system for *in situ* formation of reactive intermediate nitrile oxide from **4a** followed by its 1,3-dipolar cycloaddition reaction with alkyne **5a**. The optimization results of catalyst and sodium azide loading are shown in Table 1. In this study, a mixture of clay-Cu(II) catalyst and sodium azide in water was stirred at room temperature for 4 h, after which the reaction mixture color changed from brown to black indicating conversion of Cu(II) to Cu(I) state.[7] The treatment of hydroximyl chloride **4a** with alkyne **5a** in presence of this active catalytic system furnished desired 3,5-disubstituted isoxazole **1a** as depicted in Table 1 (entries 2-4). Catalyst loading studies indicated that 15 mol% of clay-Cu(II) catalyst and 7.5 mol% of NaN_3 was optimum, producing good yields of desired product **1a** (Table 1, entry 4). We also performed a control experiment with normal $CuSO_4$ instead of clay-Cu(II) catalyst. When 10 mol% of $CuSO_4$ and 7.5 mol% of NaN_3 were used, desired isoxazole **1a** was produced in 83% yield (entry 6). This result indicated that both Cu(II) sources are efficient, however clay-Cu(II) catalyst have recyclability advantage.

Table 1. Optimization of catalyst loading for synthesis of 3,5-disubstituted isoxazole **1a**[a]



Entry	Cu(II) catalyst (mol%)	NaN_3 (mol%)	Reaction conditions[c]	Yield[b]
1	None	None	rt, 4.5 h	0
2	Clay-Cu(II) (5)	2.5	rt, 4.5 h	52
3	Clay-Cu(II) (10)	5	rt, 4.5 h	65
4	Clay-Cu(II) (15)	7.5	rt, 4.5 h	95
5	Clay-Cu(II) (15)	0	rt, 4.5 h	0
6	$CuSO_4$ (10)	7.5	rt, 4.5 h	83

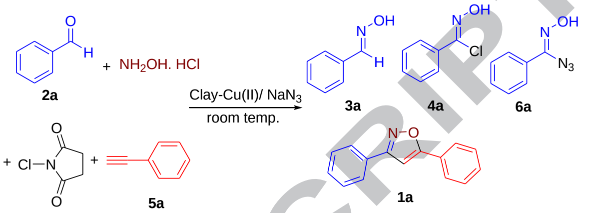
[a] A mixture of Clay-Cu(II) and NaN_3 in water was stirred for 4 h. Hydroximyl chloride **4a** and alkyne **5a** were added. Reaction further stirred for 30 min;

[b] Isolated yields after silica gel column chromatography;

[c] The combined reaction time is mentioned which includes time required to prepare Cu(I) from Cu(II) plus actual reaction time.

Next we investigated the protocol for one-pot multicomponent synthesis of 3,5-disubstituted isozaxole **1a** directly from aldehyde **2a** and alkyne **5a**. In order to optimize reaction conditions for one-pot multicomponent protocol, we investigated effect of variation in sequence of addition of substrates and reagents on formation of desired isoxazole **1a**. During this study, we investigated three methods A-C as mentioned in the Table 2. Method A involved mixing together all substrates and reagents at one time, which mainly produced intermediate oxime **3a** (entry 1) and an azido linked oxime **6a** (entries 2-3) as a major side product when reaction was performed in a mixture of water and organic solvent. In method B, the clay-Cu(II) and NaN_3 were pre-mixed in water and stirred for 4 h until the solution color changed from brown to black. The treatment of all substrates **2a**, **5a** and reagents ($NH_2OH.HCl$ and NCS) together with this prepared active clay-Cu/NaN_3 catalytic system led to the formation of desired isoxazole **1a**, but only in 20% yield (Table 2, entries 4-5). In method C, a stepwise addition of substrates and reagents was done *viz.* **2a** + $NH_2OH.HCl$, stirred for 30 min; NCS was added and stirred for 3 h; clay-Cu/NaN_3 solution and **5a** were added, stirred for 3 h. With this protocol, desired isoxazole **1a** was formed in >70% yield (Table 2, entries 6-8). Further, solvent optimization studies indicated that water: acetonitrile (1: 3) as best solvent for this one-pot multicomponent protocol (entry 8 of Table 2).

Table 2. Optimization of reaction conditions for synthesis of 3,5-disubstituted isoxazole **1a** using one-pot MCR strategy



Entry	Method	Solvent	Yield (%)			
			3a	**4a**	**6a**	**1a**
1	A	Water	80	0	0	0
2	A	Water: EtOH (1: 3)	22	0	58	0
3	A	Water: MeCN (1: 3)	25	0	62	0
4	B	Water: EtOH (1: 3)	0	55	0	18
5	B	Water: MeCN (1: 3)	0	60	0	20
6	C	Water	0	0	0	70
7	C	Water: EtOH (1: 3)	0	0	0	82
8	C	Water: MeCN (1: 3)	0	0	0	84
9	C	Water: t-BuOH (1: 1)	0	0	0	50

Method A: A mixture of aldehyde **2a** (1 mmol), $NH_2OH.HCl$ (1.2 mmol), NCS (1.3 mmol), phenylacetylene **5a** (1.3 mmol), clay-Cu(II) (15 mol%) and NaN_3 (7.5 mol%) in water stirred at rt for 6 h; Method B: Aqueous solution of clay-Cu(II) and NaN_3 (7.5 mol%) was stirred until the color changes from brown to black. To this mixture was added aldehyde **2a** (1 mmol), $NH_2OH.HCl$ (1.2 mmol), NCS (1.3 mmol), phenyl acetylene **5a** (1.3 mmol). Resulting mixture stirred for 6 h; Method C: A mixture of aldehyde **2a** (1 mmol), $NH_2OH.HCl$ (1.2 mmol) in water stirred at rt for 30 min. NCS (1.3 mmol) was added and stirred for 3 h. To this mixture was added aqueous solution of clay-Cu(II)/NaN_3 (prepared as per method B) followed by addition of phenylacetylene **5a** (1.3 mmol) and reaction mixture stirred for 3 h.[8]

Next we sought to explore the scope of this multicomponent protocol. The wide range of aromatic aldehydes/ nitrile oxides and acetylenes were investigated. Both aromatic (e.g. **1a-1e**, **1g-1n** and **1p**) and heteroaromatic aldehydes (**1f** and **1o**) participated well in this reaction. The aromatic nitrile oxides substituted with strong electron-withdrawing (e.g. –NO_2 substituted **1f** and **1o**), moderately electron-withdrawing (e.g. Cl, F substituted **1b-1e** and **1g-1n**) as well as electron-donating groups (e.g. –OMe substituted **1e**, **1j** and **1p**) produced corresponding isoxazoles in good yields. It was observed that electron-deficient nitrile oxides were preferred over electron-rich nitrile oxides in this multicomponent reaction. Amongst electron-rich benzonitrile oxides, 4-methoxy benzonitrile reacted with phenyl acetylene to produce desired isoxazole in 55% yield (example **1p**). However, other electron-rich benzonitrile oxides such as 4-hydroxy benzonitrile oxide and *p-N,N'*-dimethylamino benzonitrile oxide did not participate in this reaction. Similarly aliphatic nitrile oxides such as n-butyryl, acetyl, tert-butyryl nitrile oxides have not participated in this reaction. In these substrates, the formation of hydroximyl chloride was observed (as indicated by MS spectra), however the cycloaddition reaction was found to be the limiting step. In case of acetylene component, both aromatic (e.g. **1a-1g** and **1p**) as well as aliphatic (e.g. **1h-1o**) acetylenes participated well in this reaction. The chemical structures and yields of isoxazoles synthesized using optimized protocol (method C) are shown in Figure 2.

The clay-supported Cu(II) catalyst was characterized using XRD, SEM, TPR experiment and XPS analysis (see ESI).[7] The catalyst characterization results suggested that catalyst exists in the form of highly dispersed CuO nanoparticles supported on montmorillonite KSF (MKSF). The Cu content and total surface area of the catalyst were found to be 8.83% and 96.4551 m^2/g respectively. Analysis of catalyst-sodium azide mixtures by XPS evidenced the conversion of Cu(II) supported on clay to Cu(I) state by treatment with sodium azide.[7] This Cu(I) reacts with acetylene to form copper(I) acetylide which undergoes stepwise addition to *in situ* generated nitrile oxide furnishing 3,5-disubstituted isoxazoles. The proposed mechanism for this domino one-pot multicomponent protocol is depicted in Figure 3.

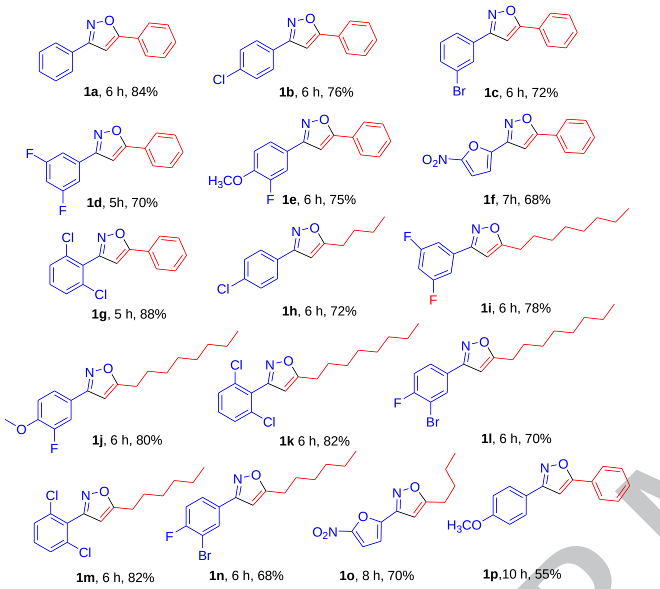


Figure 2. Isoxazoles synthesized using optimized protocol (reaction time and yields are mentioned).

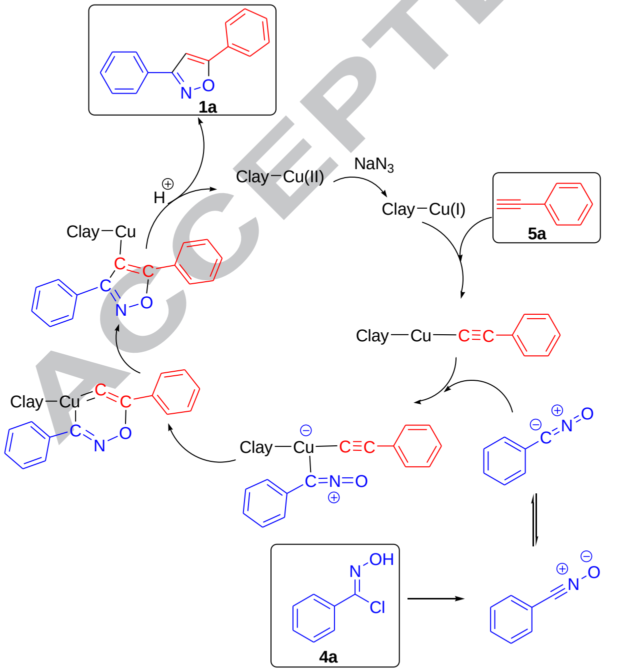


Figure 3. Plausible mechanism of one-pot multicomponent protocol for synthesis of 3,5-disubstituted isoxazole **1a** using clay-Cu(II)/NaN_3 catalyst

The clay-Cu(II) catalyst was reused repeatedly to prove its heterogeneous nature and its recyclability. The MCR between benzaldehyde (**2a**), hydroxylamine hydrochloride, *N*-chlorosuccinamide, sodium azide and phenylacetylene (**5a**) in the presence of clay-Cu(II)/NaN_3 catalytic system led to formation of isoxazole **1a** in 84, 82, 82 and 80% over four cycles respectively. In this recyclability study, catalyst was recovered by filtration after each experiment. The SEM image of the used catalyst showed similar morphology and the structural integrity after 4th run, which clearly indicated that the Clay-Cu(II) catalyst is robust, recyclable and was not affected under the reaction conditions of this MCR protocol.

In summary, we have developed a simple and efficient one-pot multicomponent protocol for regioselective synthesis of 3,5-disubstituted isoxazoles directly from aldehydes in good yields. As nitrile oxides are obtained directly from oximes, the isolation and handling of potentially harmful and unstable hydroximoyl chlorides is avoided. The clay-Cu(II) catalyst is ligand-free, leaching-free, easy to prepare, easy to handle, environmentally friendly and can be recycled several times without significant loss of catalytic activity; thus it will be highly useful for economical synthesis of 3,5-disubstituted isoxazoles.

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Supplementary material

Spectra of catalyst and all new compounds. Supplementary data associated with this article can be found, in the online version at http://www.sciencedirect.com

References and notes

1. For various pharmacological activities of isoxazoles, see: (a) Musad, E. A.; Mohamed, R.; Saeed, B. A.; Vishwanath, B. S.; Rai, K. M. L. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 3536-3540; (b) Kumar, A.; Maurya, R. A.; Sharma, S.; Ahmad, P.; Singh, A. B.; Tamrakar, A. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2009,** *17* 5285–5292; (c) Haddad, T.; Gershman, R.; Dilis, R.; Labaree, D.; Hochberg, R. B.; Hanson, R. N. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 5999-6003.
2. For references on synthesis of various isoxazoles, see: (a) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010,** *12*, 2594-2597; (b) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011,** *13*, 2966–2969; (c) Praveen, C.; Kalyanasundaram, A.; Perumal, P. T. *Synlett* **2010**, 777-781; (d) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *Org. Lett.* **2009,** *11*, 3982-3985; (e) Gayon, E.; Quinonero, O. e.; Lemouzy, S.; Vrancken, E.; Campagne, J.-M. *Org. Lett.* **2011,** *13*, 6418–6421; (f) Willy, B.; Rominger, F.; Müller, T. J. J. *Synthesis* **2008**, 293-303; (g) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011,** *13*, 5664-5667; (h) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007,** *72*, 9643-9647; (i) Crossley, J. A.; Browne, D. L. *J. Org. Chem.* **2010,** *75*, 5351-5354; (j) Sheng, S.-R.; Liu, X.-L.; Xu, Q.; Song, C.-S. *Synthesis* **2003**, 2763-2764; (k) Cecchi, L.; Sarlo, F. D.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852-4860; (l) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005,** *7*, 4487-4489; (m) Bourbeau, M. P.; Rider, J. T. *Org. Lett.* **2006,** *8*, 3679-3680; (n) Chen, C.-Y.; Andreani, T.; Li, H. *Org. Lett.* **2011,** *13*, 6300-6303; (o) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010,** *12*, 2884-2887.
3. For references on synthesis of 3,5-disubstituted isoxazoles, see: (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005,** *127*, 210-216; (b) Xu, J.; Hamme, A. T. *Synlett* **2008**, 919-923; (c) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005,**

70, 7761-7764; (d) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005,** *7*, 5203-5205.

4. (a) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2006,** *9*, 1-4; (b) Bénéteau, V.; Olmos, A.; Boningari, T.; Sommer, J.; Pale, P. *Tetrahedron Lett.* **2010,** *51*, 3673-3677; (v) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009,** *351*, 207–218; (d) Sreedhar, B.; Reddy, P. S.; Kumar, N. S. *Tetrahedron Lett.* **2006,** *47*, 3055-3058; (e) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007,** *48*, 3525–3529.
5. (a) Dadiboyena, S.; J., X.; Hamme, A. T. *Tetrahedron Lett.* **2007,** *48*, 1295-1298; (b) Sanders, B. C.; Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Arumugam, S.; Guo, J.; Boltje, T. J.; Popik, V. V.; Boons, G.-J. *J. Am. Chem. Soc.* **2011,** *133*, 949–957; (c) Jawalekar, A. M.; Reubsaet, E.; Rutjes, F. P. J. T.; Delft, F. L. v. *Chem. Commun.* **2011,** *47*, 3198–3200.
6. (a) Mudududdla, R.; Jain, S. K.; Bharate, J. B.; Gupta, A. P.; Singh, B.; Vishwakarma, R. A.; Bharate, S. B. *J. Org. Chem.* **2012,** *77*, 8821-8827; (b) Bharate, S. B.; Mudududdla, R.; Bharate, J. B.; Battini, N.; Battula, S.; Yadav, R. R.; Singh, B.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012,** *10*, 5143-5150.
7. Mohammed, S.; Padala, A. K.; Dar, B. A.; Singh, B.; Sreedhar, B.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron* **2012,** *68*, 8156-8162.
8. Typical procedure for one-pot synthesis of isoxazoles (method C): The aqueous solution of hydroxylamine hydrochloride (1.2 mmol) and aldehyde **2** (1 mmol) were stirred at room temperature for 30 min. After complete conversion of aldehyde to oxime, N-chlorosuccinamide (1.3 mmol) was added to the reaction mixture and was allowed to stir for 3 h. The clay-Cu(II)/NaN_3 mixture (prepared by stirring 15 mol% clay-Cu catalyst and 7.5 mol% NaN_3 in water until the color changes from brown to black) and phenyl acetylene **5a** (1.3 mmol) was added and the reaction mixture was further stirred for another 3 h. After completion of reaction, the reaction mixture was filtered through Whatman filter paper, residue was washed with EtOAc. Organic layer was separated from filtrate and was dried over anhydrous sodium sulfate. Combined organic layers were concentrated in vacuo and crude reaction mixture was purified by silica gel (#100-200) column chromatography using EtOAc: hexane as eluting solvent to get corresponding 3,5-disubstituted isoxazoles **1a-1o** in 68-88% yield. Spectral data of all compounds is provided in supplementary material. The spectral data of representative two compounds is provided here. **1f**: Yield: 68%; yellow solid; m.p. 190-193 ^{o}C; Rf (5% EtOAc: n-hexane) 0.18; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82-7.84 (m, 2H). 7.49-7.51 (m, 3H), 7.46 (d, *J* = 3.8 Hz, 1H), 7.24, (d, *J* = 3.8 Hz, 1H), 6.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.57, 153.84, 146.63, 130.97, 129.21, 126.46, 126.00, 113.09, 111.97, 97.20; IR (neat): ν_{max} 3435, 3118, 2923, 2851, 1616, 1570, 1514, 1363, 1025 cm^{-1}; ESI-MS: m/z 257.013 $[M+1]^+$; HRMS (ESI+): m/z 257.0554 calcd for $C_{13}H_8N_2O_4$+H^+ (257.0557). **1h**: Yield: 72%; colorless liquid; Rf (5% EtOAc: n-hexane) 0.54; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, J = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.20 (s, 1H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.80-1.70 (m, 2H), 1.48-1.38 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz,): δ 174.08, 160.79, 135.18, 128.55, 127.44, 127.36, 98.09, 29.01, 25.93, 21.63, 13.14; IR (neat): ν_{max} 2959, 2931, 2872, 1604, 1569, 1509, 1456, 1427, 1092, 1015 cm^{-1}; ESI-MS: *m/z* 236.0373 $[M+1]^+$; HRMS (ESI+): *m/z* 236.0832 calcd for $C_{13}H_{14}ClNO$ + H^+ (236.0837).