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Original article

Synthesis of 3,5-diarylisoxazoles under solvent-free conditions using iodobenzene diacetate

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ABSTRACT

A simple and efficient method has been developed for conversion of chalcone oximes to 3,5-diaryl isoxazoles in excellent yields under solvent-free conditions. The synthesized compounds were characterized by infrared spectroscopy, ^{1}H NMR, ^{13}C NMR and HRMS.

1. Introduction

Isoxazoles represent an important class of aromatic heterocycles, and are associated with a wide spectrum of biological activities, such as antiviral [1], antimicrobial [2], anti-inflammatory [3], anticonvulsant [4], antihyperglycemic [5], anticancer [6] activity, *etc*.

In general, isoxazoles are obtained by two major routes: [3+2] cycloaddition of alkenes/alkynes with nitrile oxides, or the reaction of hydroxylamine with a three-carbon atom component [7,8]. Recently, synthesis of 3,5- and 3,4-disubstituted isoxazoles through transition-metal-catalyzed [3+2] cycloaddition reactions was also reported [9]. To date, a variety of other methods have also been reported for synthesis of isoxazoles [10].

3,5-Diarylisoxazoles are also synthesized regioselectively by the reaction of chalcones with hydroxylamine hydrochloride using K_2CO_3 as solid support under microwave conditions [11]. However, these methods usually are of limited scope and use harsh conditions. Recently, organic reactions under solvent-free conditions have received much attention due to advantages over the conventional methods in terms of time, yields and relatively benign conditions [12]. Presently, there is also a considerable interest in organohypervalent iodine reagents because of their versatile use in solid-state organic reactions [12]. These reagents are used in the synthesis of several heterocyclic compounds in liquid and solid state [13].

In view of the above interest in these compounds and in continuation of our studies on the cyclization of heterocyclic compounds [14] we undertook to develop an efficient and environmentally benign synthesis of 3,5-diarylisoxazoles that proceed under solvent-free conditions. Herein, we report results on the transformation of various substituted chalcone oximes to 3,5-diarylisoxazoles (Scheme 1) with iodobenzene diacetate that leads to the expeditious formation of the title compounds in very good yields. Chalcone oximes are prepared as per the literature protocol [10f,g]. To the best of our knowledge, there is no report on the synthesis of 3,5-diarylisoxazoles under solvent free conditions.

2. Experimental

All starting materials were purified by standard methods before use. All yields refer to isolated products after purification. Melting points were determined in open capillaries using Büchi 530 melting point apparatus without correction. The reactions were monitored and the purity of the compounds checked by ascending thin layer chromatography (TLC) on silica gel coated aluminium plates (Merck 60 F254, 0.25 mm) using mixture of chloroform and methanol. The developed plates were visualized under ultra violet light at 254 and 366 nm. Infrared (IR) spectra were recorded as KBr discs on a Schimadzu IR Prestige-21 FT-IR spectrophotometer

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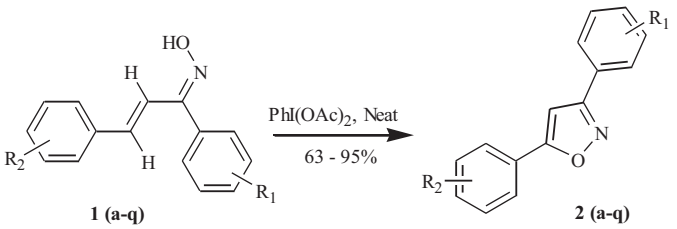


Scheme 1. Synthesis of 3,5-diarylisoxazoles (**2a–q**).

(cm^{-1}). ^1H NMR spectra were recorded on a Bruker DRX400 spectrometer using tetramethylsilane as internal standard, chemical shifts in ppm. Mass spectra were recorded on a VG-70-S mass spectrometer.

*General procedure for synthesis of 3,5-diarylisoxazoles (***2 a–q***)*: A mixture of chalcone oxime (1 mmol) and iodobenzene diacetate (1.2 mmol) was ground thoroughly in a pestle and mortar. After 2–3 min, an exothermic reaction ensued while in some cases slightly warming to ~40 °C for 2 min was required to initiate the reaction. The residue was washed with hexane and then recrystallized, or filtered through a small pad of silica gel, to afford analytically pure products. All the known compounds were identified by comparison of their melting points, ^1H NMR, ^{13}C NMR data with the literature data.

*5-(4-Chlorophenyl)-3-(4-nitrophenyl) isoxazole (***2e***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–8.07 (m, 4H), 7.48–7.53 (m, 4H), 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 162.3, 151.2, 139.1, 134.3, 129.3, 128.9, 128.6, 127.8, 124.3, 99.7. HRMS calcd. for $C_{15}H_9ClN_2O_3$: 300.0302, found: 300.0301. IR (KBr, cm^{-1}): ν 813 and 828 (OOP *para* substituent), 1618 (C=N).

*3-(4-Chlorophenyl)-5-(3-nitrophenyl) isoxazole (***2i***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.68–7.89 (m, 4H), 7.78–7.46 (m, 4H), 6.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 162.6, 145.2, 133.5, 131.6, 130.6, 129.8, 128.9, 127.8, 124.3, 123.5, 122.7, 96.5. HRMS calcd. for $C_{15}H_9ClN_2O_3$ 300.0302, found 300.0299. IR (KBr, cm^{-1}): ν 816, 782 and 703 (OOP *para* substituent), 1611 (C=N).

*5-(2,6-Dichlorophenyl)-3-(4-methylphenyl) isoxazole (***2m***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.52–8.54 (d, 2H), 7.88–7.84 (s, 1H), 7.63–7.61 (d, 2H), 7.48–7.46 (d, 2H), 6.92 (s, 1H), 2.6 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.1, 151.4, 146.3, 140.3, 132.7, 130.2, 129.1, 128.8, 126.9, 124.5, 115.6, 94.5, 22.9. HRMS calcd. for $C_{16}H_{11}Cl_2NO$ 304.1706, found 304.1729. IR (KBr, cm^{-1}): ν 823 (OOP *para* substituent), 1623 (C=N).

*5-(2,3-Dichlorophenyl)-3-(4-methylphenyl) isoxazole (***2n***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.61–8.67 (m, 1H), 7.82–7.78 (m, 1H), 7.76 (m, 1H), 7.58–7.56 (d, 2H), 7.39–7.37 (d, 2H), 6.83 (s, 1H), 2.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 164.2, 149.4, 138.3, 132.1, 129.6, 125.2, 121.3, 119.8, 116.3, 115.5, 113.2, 98.7, 24.3. HRMS calcd. for $C_{16}H_{11}Cl_2NO$: 304.1706, found: 304.1711. IR (KBr, cm^{-1}): ν 799 (OOP *para* substituent), 1629 (C=N).

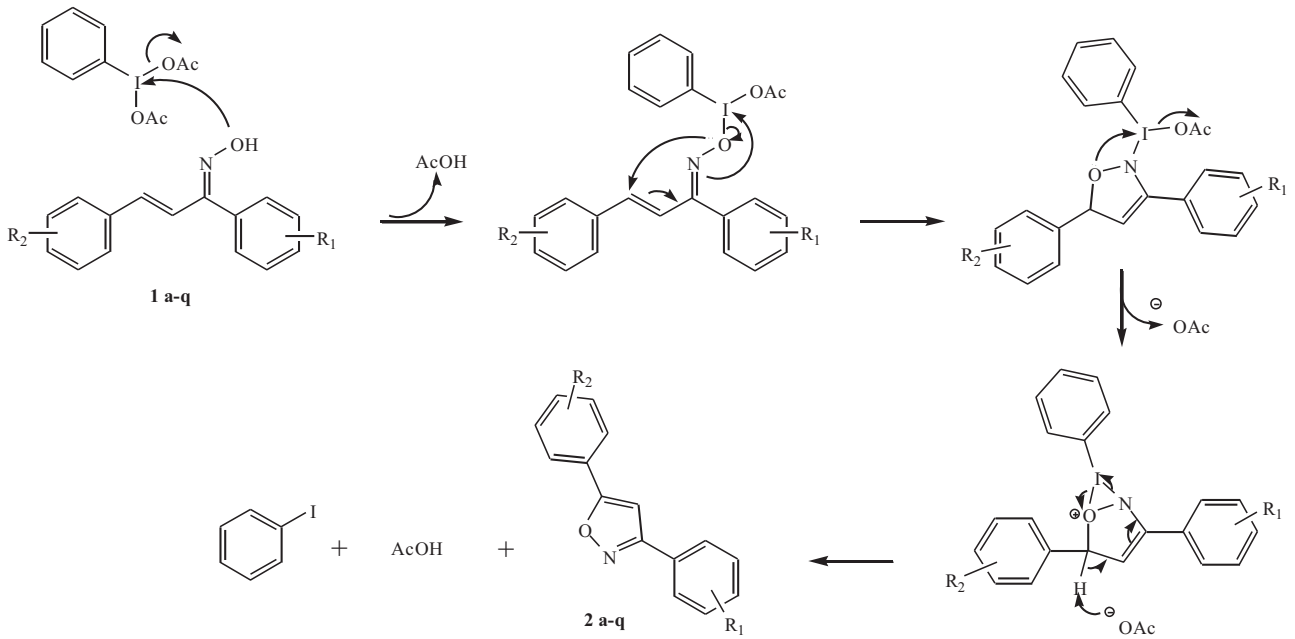
*5-(2,4-Dichlorophenyl)-3-(4-methylphenyl) isoxazole (***2o***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.72–8.69 (s, 1H), 8.02–8.05 (d, 1H), 7.87–7.89 (d, 1H), 7.57–7.59 (d, 2H), 7.48–7.51 (d, 2H), 6.97 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 165.2, 148.7, 135.3, 131.8, 129.1, 127.6, 126.5, 125.7, 122.5, 121.2, 115.3, 96.5, 25.3. HRMS calcd. for $C_{16}H_{11}Cl_2NO$: 304.1706, found: 304.1734. IR (KBr, cm^{-1}): ν 806 (OOP *para* substituent), 1627 (C=N).

*5-(2,4-Dichlorophenyl)-3-(2-methoxyphenyl) isoxazole (***2p***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.57–8.52 (s, 1H), 7.93–7.98 (d, 1H), 7.61–7.68 (d, 1H), 7.26–7.29 (m, 2H), 7.15–7.18 (m, 1H), 7.05–7.08 (m, 1H), 6.81 (s, 1H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 165.8, 150.7, 142.6, 138.3, 133.3, 130.1, 129.3, 127.9, 126.8, 125.7, 123.5, 121.2, 118.3, 94.1, 57.3. HRMS calcd. for $C_{16}H_{11}Cl_2NO_2$: 300.0302, found: 300.0299. IR (KBr, cm^{-1}): ν 763 (OOP *ortho* substituent), 1123 & 1186 (C-O), 1621 (C=N).

*5-(2,3-Dichlorophenyl)-3-(2-methoxyphenyl) isoxazole (***2q***)*: ^1H NMR (400 MHz, $CDCl_3$): δ 8.62–8.65 (m, 1H), 8.12–8.17 (m, 1H), 7.83–7.87 (m, 1H), 7.32–7.35 (m, 2H), 7.19–7.23 (m, 1H), 7.02–7.07 (m, 1H), 6.76 (s, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 164.1, 149.7, 139.3, 136.2, 132.6, 129.4, 128.9, 127.7, 126.3, 125.7, 123.3, 122.7, 119.3, 95.2, 53.7. HRMS calcd. for $C_{16}H_{11}Cl_2NO_2$: 300.0302, found: 300.0299. IR (KBr, cm^{-1}): ν 779 (OOP *ortho* substituent), 1082 & 1167 (C-O), 1619 (C=N).

3. Results and discussion

This conversion simply involves a thorough mixing of substrates with iodobenzene diacetate at room temperature



Scheme 2. The plausible mechanism for the formation of the product.

Table 1
Physical properties of 3,5-diarylisoxazoles (**2a–q**).

Compd.	R_1	R_2	Yield (%)	Mp (°C)	Lit. mp (°C) or mol. formula
2a	H	4-Cl	95	177–178	178–179 [16a,d]
2b	H	4-NO_2	85	220–222	222 [16b]
2c	H	4-Br	92	175–177	177–179 [16c]
2d	H	4-OCH_3	78	126–127	126–128 [16c]
2e	4-Cl	4-NO_2	92	230–232	$C_{15}H_9ClN_2O_3$
2f	4-OCH_3	4-Cl	91	185–186	188 [16d]
2g	4-OCH_3	4-NO_2	82	214–216	217 [16d]
2h	4-NO_2	4-Cl	82	147–149	148–150 [16c]
2i	3-NO_2	4-Cl	76	140–142	$C_{15}H_9ClN_2O_3$
2j	4-NO_2	4-NO_2	84	286–287	286–288 [16a]
2k	4-Br	4-NO_2	88	221–222	222–223 [16a]
2l	4-Br	4-Cl	90	200–201	198–200 [16a]
2m	4-Me	2,6-dichloro	63	214–215	$C_{16}H_{11}Cl_2NO$
2n	4-Me	2,3-dichloro	72	205–207	$C_{16}H_{11}Cl_2NO$
2o	4-Me	2,4-dichloro	81	184–186	$C_{16}H_{11}Cl_2NO$
2p	2-OMe	2,4-dichloro	76	163–165	$C_{16}H_{11}Cl_2NO_2$
2q	2-OMe	2,3-dichloro	73	181–183	$C_{16}H_{11}Cl_2NO_2$

(slightly warming in some cases) *via* an exothermic reaction. Chalcone oximes form a yellowish eutectic melt with iodobenzene diacetate upon mixing *prior to* the occurrence of a mildly exothermic reaction. This is in accordance with the postulated model for such solid–solid reactions [14b,15].

The IR spectrum of compound **2e** showed an absorption at ν_{max} = 827–832 cm^{-1} (aromatic C–H OOP bending {para}), 1344 and 1510 cm^{-1} (aromatic nitro), 1618 cm^{-1} (C=N stretch). In the ^1H NMR spectrum, the only proton of the isoxazole nucleus resonated as a sharp singlet at δ 6.81 and the aromatic protons were seen as a multiplet at δ 7.48–8.07. In the ^{13}C NMR, signals appeared at δ 169.8, 162.3, 151.2, 139.1, 134.3, 129.3, 128.9, 128.6, 127.8, 124.3, 99.7. The high resolution mass spectra of this compound exhibited the molecular ion peak at *m/z* 300.0301 which is in agreement with the calculated value 300.0302.

Under optimized conditions, syntheses of 3,5-diarylisoxazoles, **2a–q**, were undertaken. All the melting points of synthesized compounds (Table 1) were in agreement with the melting points found in the literature [16]. The plausible mechanism for the formation of the product is outlined in Scheme 2.

4. Conclusion

In conclusion, we have developed a simple, benign and expeditious synthesis of biologically significant 3,5-diarylisoxazoles in good yields under solvent-free conditions and fully characterized the products.

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References

[1] V.A. Makarov, O.B. Riabova, V.G. Granik, P. Wutzler, M. Schmidtke, Novel [(biphenyloxy)propyl]isoxazole derivatives for inhibition of human rhinovirus 2 and coxsackievirus B3 replication, J. Antimicrob. Chemother. 5 (2005) 483–488.
[2] A. Padmaja, T. Payani, G. Dinneswara Reddy, V. Padmavathi, Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives, Eur. J. Med. Chem. 44 (2009) 4557–4566.
[3] G. Amgad, P.N. Habeeb, R. Praveen, E.E. Knaus, Design and synthesis of 4,5-diphenyl-4-isoxazolines: novel inhibitors of cyclooxygenase-2 with analgesic and antiinflammatory activity, J. Med. Chem. 44 (2001) 2921–2927.
[4] S. Balalaie, A. Sharifi, B. Ahangarian, Solid phase synthesis of isoxazole and pyrazole derivatives under microwave irradiation, Indian J. Heterocycl. Chem. 10 (2000) 149–150.
[5] A. Kumar, R.A. Maurya, S. Sharma, et al., Design and synthesis of 3,5-diarylisoxazole derivatives as novel class of anti-hyperglycemic and lipid lowering agents, Bioorg. Med. Chem. 17 (2009) 5285–5292.
[6] P. Diana, A. Carbone, P. Barraja, et al., Synthesis and antitumor activity of 2,5-bis(3′-indolyl)-furans and 3,5-bis(3′-indolyl)-isoxazoles, nortopsentin analogues, Bioorg. Med. Chem. 18 (2010) 4524–4529.
[7] (a) E. Schaumann, in: E. Schaumann (Ed.), Science of Synthesis, Houben–Weyl methods of molecular transformations, Georg Thieme Verlag, Stuttgart, 2001, pp. 229–288;
(b) T.M.V.D. Pinho eMelo, Recent advances on the synthesis and reactivity of isoxazoles, Curr. Org. Chem. 9 (2005) 925–958.
[8] V. Jager, P.A. Colinas, in: A. Padwa, W.H. Pearson (Eds.), Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Wiley, Hoboken, 2002, pp. 361–472.
[9] (a) F. Himo, T. Lovell, R. Hilgraf, et al., Copper (I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates, J. Am. Chem. Soc. 127 (2005) 210–216;
(b) T.V. Hansen, P. Wu, V.V. Fokin, One-pot copper(I)-catalyzed synthesis of 3,5-disubstituted isoxazoles, J. Org. Chem. 70 (2005) 7761–7764;
(c) S. Grecian, V.V. Fokin, Ruthenium-catalyzed cycloaddition of nitrile oxides and alkynes: practical synthesis of isoxazoles, Angew. Chem. Int. Ed. 47 (2008) 8285–8287.
[10] (a) G. Pellegrino, F. Leonetti, A. Carotti, et al., Solid phase synthesis of a molecular library of pyrimidines, pyrazoles, and isoxazoles with biological potential, Tetrahedron Lett. 51 (2010) 1702–1705;
(b) B. Girardin, P.G. Alsabeh, S. Lauzon, S.J. Dolman, S.G. Ouellet, G. Hughes, Synthesis of 3-aminoisoxazoles via the addition—elimination of amines on 3-bromoisoxazolines, Org. Lett. 11 (2009) 1159–1162;
(c) J.P. Xu, A.T. Hamme II, Efficient access to isoxazoles from alkenes, Synlett 6 (2008) 919–923;
(d) F.A. Rosap, P. Machado, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, Reaction of β-dimethylaminovinyl ketones with hydroxylamine: a simple and useful method for synthesis of 3- and 5-substituted isoxazoles, J. Heterocycl. Chem. 45 (2008) 879–885;
(e) J.P. Waldo, R.C. Larock, The synthesis of highly substituted isoxazoles by electrophilic cyclization: an efficient synthesis of valdecoxib, J. Org. Chem. 72 (2007) 9643–9647;
(f) R.F. Kurangi, R. Kawthankar, S. Sawal, V.G. Desai, S.G. Tilve, Convenient synthesis of 3,5-disubstituted isoxazoles, Synth. Commun. 37 (2007) 585–587;
(g) V.G. Desai, S.G. Tilve, A novel and convenient method for the synthesis of 3,5-diarylisoxazoles, Synth. Commun. 29 (1999) 3017–3020;
(h) J.P. Waldo, R.C. Larock, Synthesis of isoxazoles via electrophilic cyclization, Org. Lett. 23 (2005) 5203–5205.
[11] M. Kidwai, S. Kukreja, R. Thakur, K_2CO_3 mediated regioselective synthesis of isoxazoles and pyrazolines, Lett. Org. Chem. 3 (2006) 135–139.
[12] (a) M.A.P. Martins, C.P. Frizzo, D.N. Moreira, L. Buriol, P. Machado, Solvent-free heterocyclic synthesis, Chem. Rev. 109 (2009) 4140–4182;
(b) A. Rostami, J.A. Akradi, Highly efficient, green, rapid and chemoselective oxidation of sulfides using hydrogen peroxide and boric acid as the catalyst under solvent-free conditions, Tetrahedron Lett. 51 (2010) 3501–3503;
(c) G. Epane, J.C. Laguerre, A. Wadouachi, A. Marek, Microwave-assisted conversion of D-glucose into lactic acid under solvent-free condition, Green Chem. 12 (2010) 502–506;
(d) V. Polshettiwar, R.S. Varma, Ring-fused aminals, catalyst and solvent-free microwave-assisted α amination of nitrogen heterocycles, Tetrahedron Lett. 49 (2008) 7165–7167;

(e) K. Tanaka, F. Toda, Solvent-free organic synthesis, Chem. Rev. 100 (2000) 1025–1074.

[13] (a) O. Prakash, M. Kumar, R. Kumar, C. Sharma, K.R. Aneja, Hypervalent iodine(III) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents, Eur. J. Med. Chem. 45 (2010) 4252–4257;
(b) K. Niedermann, J.M. Welch, R. Koller, et al., New hypervalent iodine reagents for electrophilic trifluoromethylation and their precursors: synthesis, structure and reactivity, Tetrahedron 66 (2010) 5753–5761;
(c) B.A. Mendelsohn, S. Lee, S. Kim, et al., Oxidation of oximes to nitrile oxides with hypervalent iodine reagent, Org. Lett. 11 (2009) 1539–1542;
(d) F. Felpin, Oxidation of 4-arylphenol trimethylsilyl ethers to p-arylquinols using hypervalent iodine(III) reagents, Tetrahedron Lett. 48 (2007) 409–412;
(e) C.B. Singh, H. Ghosh, S. Murru, B.K. Patel, Hypervalent iodine(III)-mediated regioselective N-acylation of 1,3-disubstituted thioureas, J. Org. Chem. 73 (2008) 2924–2927;
(f) V.V. Zhdankin, P.J. Stang, Recent developments in the chemistry of polyvalent iodine compounds, Chem. Rev. 102 (2002) 2523–2584.

[14] (a) K.V.G. Chandra Sekhar, V.S. Rao, M.M.K. Kumar, Design, synthesis and preliminary in vitro and in vivo pharmacological evaluation of 2-{4-[4-(2,5-disubstitutedthiazol-4-yl)phenylethyl]piperazin-1-yl}-1,8-naphthyridine-3-carbonitriles as atypical antipsychotic agents, J. Enzyme Inhib. Med. Chem. 24 (2009) 871–875;
(b) D. Kumar, K.V.G. Chandra Sekhar, H. Dhillon, V.S. Rao, R.S. Varma, An expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo [4,3-a] quinoxalines under solvent-free conditions using iodobenzene diacetate, Green Chem. 6 (2004) 156–157;
(c) V.S. Rao, K.V.G. Chandra Sekhar, Iodobenzene diacetate mediated solid-state synthesis of heterocyclic 1,3,4-oxadiazoles, Synth. Commun. 34 (2004) 2153–2157.

[15] G. Rothenberg, A.P. Downie, C.L. Raston, J.L. Scott, Understanding solid/solid organic reactions, J. Am. Chem. Soc. 123 (2001) 8701–8708.

[16] (a) X. Wei, J. Fang, Y. Hu, H. Hu, Convenient preparation of 3,5-diarylisoxazoles, Synthesis 12 (1992) 1205–1206;
(b) F. Himo, T. Lovell, R. Hilgraf, et al., Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates, J. Am. Chem. Soc. 127 (2005) 210–216;
(c) S. Tang, J. He, Y. Sun, L. He, X. She, Efficient and regioselective one-pot synthesis of 3-substituted and 3,5-disubstituted isoxazoles, Org. Lett. 11 (2009) 3982–3985;
(d) A.Y. Deshmukh, P.B. Raghuwanshi, A.G. Doshi, Synthesis and dehydrogenation of isoxazolines by using DMSO-I_2-H_2SO_4 and DMSO-I_2 system, Asian J. Chem. 14 (2002) 548–550.