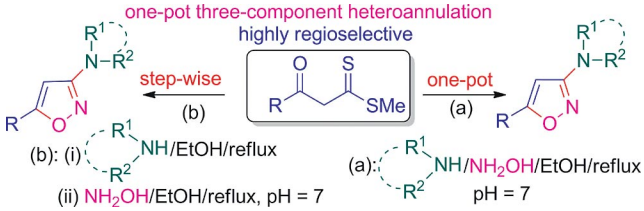
EurJOC European Journal of Organic Chemistry

Isoxazole Synthesis



A highly regioselective synthesis of 5-substituted 3-aminoisoxazoles has been achieved by a one-pot three-component coupling of β-oxo dithioesters, amines and hydroxylamine in ethanol at reflux via an in situ generated β-oxo thioamide intermediate. The mechanism of the reaction has been established experimentally and shown to be in agreement with the HSAB theory.

Keywords: Amines / Multicomponent reactions / Heteroannulation / Heterocycles / Regioselectivity

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One-Pot Three-Component Heteroannulation of β-Oxo Dithioesters, Amines and Hydroxylamine: Regioselective, Facile and Straightforward Entry to 5-Substituted 3-Aminoisoxazoles

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Keywords: Amines / Multicomponent reactions / Heteroannulation / Heterocycles / Regioselectivity

An efficient and highly regioselective one-pot three-component synthesis of previously inaccessible and synthetically demanding 3-(cycloalkyl/alkyl/arylamino)-5-aryl/alkylisoxazoles has been achieved by the cyclocondensation of β-oxo dithioesters, amines and hydroxylamine in ethanol at reflux. This transformation proceeds via an in situ generated β-oxothioamide by the reaction of the β-oxo dithioester and amine, which undergoes nucleophilic attack by hydroxylamine followed by intramolecular cyclization with the oxo functionality and subsequent dehydration to give 5-substituted 3-aminoisoxazoles as a single regioisomer in good yields. Furthermore, the mechanism of the reaction has been established experimentally and shown to be in agreement with the hard and soft (Lewis) acid and base (HSAB) theory.

Introduction

Of the five-membered nitrogen heterocycles, isoxazole and its derivatives have received considerable attention during the last few decades because of their rich chemistry[1] and broad spectrum of pharmacological properties, such as analgesic, anti-inflammatory, hypoglycemic, anti-bacterial, antinociceptive and anti-cancer activities.[2] Substituted isoxazoles, which are embedded as core structures in several natural products (e.g., ibotenic acid, muscimol and isoxazole-4-carboxylic acid) and commercial drugs[3] (e.g., valdecoxib, bradykinin, leflunomide and oxacillins), are important synthetic targets. Some isoxazole derivatives also serve as linkers in probes for live cells.[4] Furthermore, isoxazoles containing aryl and carboxamide groups have been shown to have potent in vivo anti-thrombotic efficacy and to be a platelet-activating factor (PAF) antagonist.[4c] In addition, many substituted isoxazoles are used in the agrochemical industry[5] as pesticides and insecticides. Notably, many isoxazole derivatives have been utilized as semi-conductors, single-walled nanotubes, liquid crystals, chiral ligands, scaffolds for peptidomimetics, dyes and high-temperature lubricants.[6] Moreover, suitably substituted isoxazoles also serve as versatile building blocks in organic synthesis as they can be converted into several valuable synthons, such as β-hydroxy ketones, β-hydroxy nitriles, γ-amino alcohols and α,β-unsaturated oximes.[7]

Several elegant approaches to isoxazoles have been reported in the literature, and the major routes typically involve the 1,3-dipolar cycloaddition of alkenes/alkynes and nitrile oxides,[8] the intramolecular cyclization of ketoximes/propargylic oximes[9] and the reaction of hydroxylamine with α-acetylenic ketones/aldehydes, β-oxo esters, α,β-unsaturated ketones, propargylic alcohols and β-oxo nitriles.[10] Although various synthetic methods for the synthesis of disubstituted isoxazoles have been developed,[11] regioselective control of the functionalization of isoxazole is still the main concern. Recently, Carreira and co-workers synthesized substituted isoxazoles by base-mediated rearrangement of oxetanes.[12] Delft and co-workers developed a metal-free regioselective synthesis of 3,5-disubstituted isoxazoles by the hypervalent iodine-induced cycloaddition of nitrile oxides to alkynes.[13] Chen and co-workers revealed a palladium-catalysed cascade cyclization/alkenylation sequence for the synthesis of 3,4,5-trisubstituted isoxazoles,[14a] and in a recent paper Xie and co-workers reported the synthesis of 2,3-dihydroxyisoxazoles by domino reactions in water.[14b] Nitro/dinitro dienes have been successfully used to synthesize 3,5-disubstituted isoxazoles.[14c–14h] Despite their high biological activity, there are very few reports on the synthesis of substituted 3-aminoisoxazoles,[15] and very few of these methods are general, regioselective and high yielding, the majority of them not being very reliable or efficient. Typical problems incurred in the synthesis of aminoisoxazoles include poor yields, multiple steps and low selectivity between the formation of

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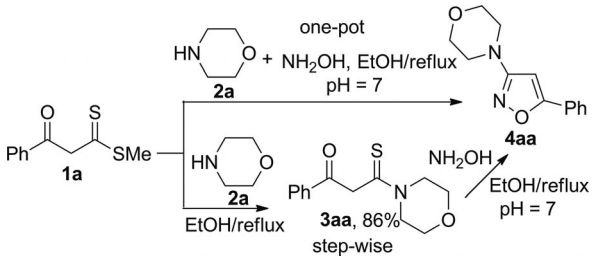
3-amino- and 5-aminoisoxazoles.[16] Therefore a robust, practical, catalyst-free, regioselective method for the synthesis of aminoisoxazoles with broad scope is highly desirable.

The concept of multicomponent reactions (MCRs) involving a domino process with at least three different simple substrates has experienced exponential growth over the last decade and emerged as a powerful strategy for the rapid generation of molecular complexity and diversity.[17] There has been a considerable revival of interest in the synthesis of amino-substituted isoxazoles,[18] because they are key building blocks in many naturally occurring molecules and pharmaceutically active synthetic compounds[19] and serve as useful precursors for condensed bioactive heterocycles. During the course of our one-pot reactions directed towards synthetic applications of β-oxo dithioesters in heterocyclic synthesis,[20] we have developed a highly regioselective one-pot three-component protocol for the facile synthesis of 5-substituted 3-aminoisoxazoles by the coupling of β-oxo dithioesters, amines and hydroxylamine under mild reaction conditions. The results of these studies are reported herein.

Results and Discussion

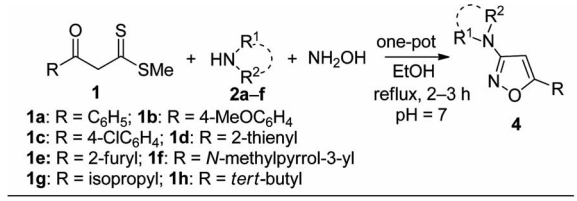
β-Oxo dithioesters are not commercially available and were prepared according to reported procedures.[21a,21b] Their use as versatile intermediates in organic synthesis is well recognized due to the presence of two electrophilic and three nucleophilic reactive sites, which can be exploited in a regioselective manner.[20,21] Although isoxazole derivatives have been synthesized from S,S-/N,S-acetals[22a–22e] and β-oxo esters,[22f] so far, to the best of our knowledge, there is no report on the synthesis of isoxazoles from β-oxo dithioesters. Therefore, we set out to explore the feasibility of β-oxo dithioesters as 1,3-dielectrophilic synthons to access isoxazoles.

Thus, when methyl 3-oxo-3-phenylpropanedithioate (**1a**; 1.0 equiv.) was treated with morpholine (**2a**; 1.2 equiv.) and neutral hydroxylamine (4.0 equiv., generated by the reaction of equimolar amounts of $NH_2OH·HCl$ and KOH in water) in ethanol at reflux for 2 h (monitored by TLC) in a one-pot three-component procedure, workup of the reaction mixture afforded 3-morpholino-5-phenylisoxazole (**4aa**) in 71% yield (Scheme 1; Table 1, Entry 1). An alternative stepwise approach was also performed. Thus, in another experiment, **1a** (1.0 equiv.) was treated with morpholine (**2a**; 1.2 equiv.) in ethanol at reflux for 2 h to afford β-oxo thioamide **3aa** in 86% yield, which was found to be identical to our previously reported sample.[20d] Treatment of the pure thioamide **3aa** with neutral hydroxylamine



Scheme 1. One-pot and stepwise syntheses of 3-morpholino-5-phenylisoxazole (**4aa**).

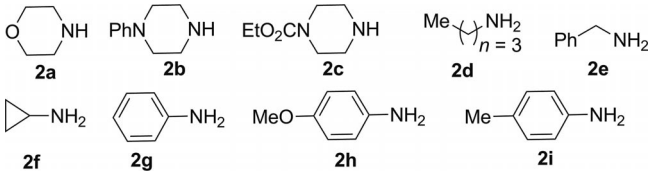
Table 1. One-pot synthesis of 3-alkylamino-5-aryl/alkylisoxazoles **4**.



Entry	Product (yield [%])	Entry	Product (yield [%])
1	**4aa** (71)	11	**4bf** (68)
2	**4ab** (69)	12	**4bh** (64)
3	**4ac** (73)	13	**4ca** (66)
4	**4ad** (68)	14	**4cb** (76)
5	**4ae** (72)	15	**4cd** (66)
6	**4af** (72)	16	**4ce** (66)
7	**4ag** (69)	17	**4da** (70)
8	**4ba** (68)	18	**4db** (67)
9	**4bd** (71)	19	**4ea** (70)
10	**4be** (68)	20	**4fd** (48)

(4.0 equiv.) in ethanol at reflux for 2 h furnished isoxazole **4aa** in a comparable yield (73%) as a single regioisomer (Scheme 1).

To elaborate the scope of the reaction, the above one-pot three-component procedure was applied to the synthesis of other 5-substituted 3-(cycloamino)isoxazoles **4** as single regioisomers in good yields by using various β-oxo dithioesters **1a**–**h** and cyclic secondary or primary aliphatic amines **2a**–**2f** (Scheme 2; Table 1). The reaction tolerated a broad range of functional groups on both the β-oxo dithioester and amine. The cyclocondensation protocol was found to be equally facile with aliphatic β-oxo dithioesters **1g** and **1h** derived from isopropyl methyl ketone and *tert*-butyl methyl ketone, respectively, and furnished the corresponding 3-cycloamino-5-alkylisoxazoles **4ag** and **4bh** in yields of 69 and 64% under conditions identical to those described above (Table 1, Entries 7 and 12).



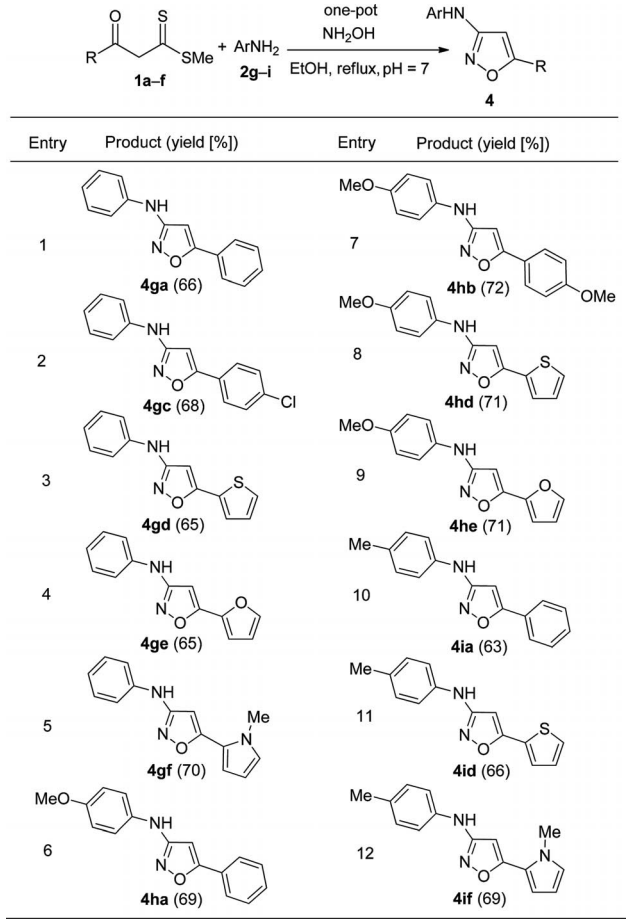
Scheme 2. Different amine substrates **2** used in the synthesis of 3-alkylamino-5-aryl/alkylisoxazoles **4**.

We then extended our study to aromatic amines with a view to adding further diversity at the 3-position of the isoxazole ring. Thus, when β-oxo dithioester **1a** was treated with aniline **2g** and NH_2OH under the previously described one-pot conditions, 3-anilino-5-phenylisoxazole (**4ga**) was obtained in 66% yield (Table 2, Entry 1). The generality of the reaction was established by synthesizing 12 different 3-arylamino-5-arylisoxazoles **4** by cyclocondensation of the appropriate β-oxo dithioesters **1a**–**f** with aromatic amines **2g**–**i** and hydroxylamine under identical reaction conditions (Table 2). Notably, the reactions of the aromatic amines took longer to complete than the reactions with aliphatic amines.

The structures of all the synthesized isoxazoles **4** were confirmed by spectral studies, and their regiochemistry was confirmed by single-crystal X-ray analysis of representative compounds **4ac**, **4af**, **4gc** and **4bh** (Figure 1).[23] Thus, by using this three-component one-pot procedure, we have synthesized a small library (32 compounds) of previously unknown 5-substituted 3-(cycloamino/alkylamino/arylamino)isoxazoles in good yields and with high purity.

To illustrate the broad synthetic utility and generality of our developed methodology, we undertook the formal synthesis of annulated isoxazoles. Thus, we treated cyclic β-oxo dithioesters derived from α-tetralone and cyclohexanone (**1i** and **1j**, respectively) with cyclic secondary amines **2a**, **2b** and **2c** separately and hydroxylamine under the previously described conditions. Unfortunately, workup of the reaction provided the corresponding thioamides **3ai**, **3ci** and **3bj** in

Table 2. Synthesis of 3-arylamino-5-arylisoxazoles **4**.



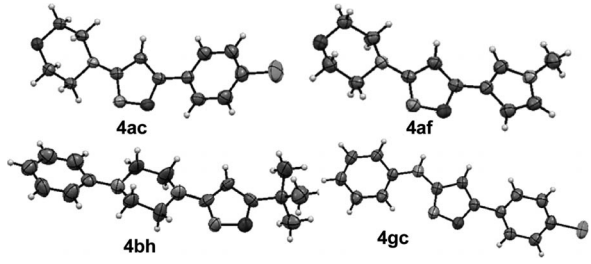
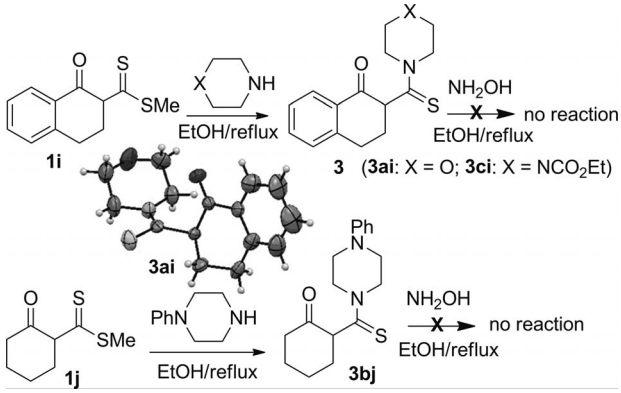


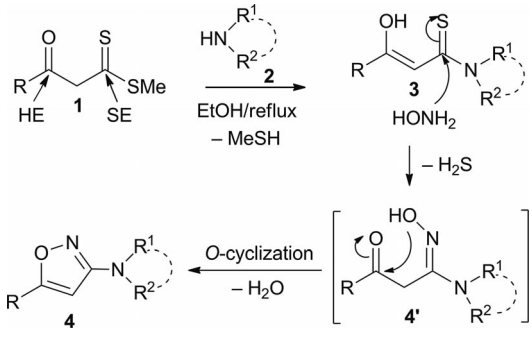
Figure 1. ORTEP diagrams of **4ac**, **4af**, **4bh** and **4gc**.

quantitative yields with no traces of the desired isoxazoles. Furthermore, the thioamide **3ai** thus obtained was treated with excess of the neutral hydroxylamine (6.0 equiv.) in ethanol at reflux for 18 h, and still no trace of the desired isoxazole was formed, but the thioamide was completely recovered (Scheme 3). The X-ray crystal structure of β-oxo thioamide **3ai** displays an *anti* orientation of the carbonyl and thiocarbonyl groups.[23] Thus, it may be inferred that the formation of isoxazole is not possible due to the orientation of the carbonyl and thiocarbonyl groups, limiting the scope of the reaction to some extent.



Scheme 3. Attempted synthesis of annulated isoxazoles.

Based on literature reports and our experimental results, we propose the reaction mechanism outlined in Scheme 4. The carbonyl and thiocarbonyl carbon atoms in β-oxo dithioester **1** can be regarded as relatively hard and soft electrophilic centres, respectively, because the carbonyl carbon atom is adjacent to the hard oxygen centre and the thiocarbonyl carbon atom is flanked by the soft thiomethyl group. First, β-oxo dithioester **1** reacts with amine **2** to generate β-oxo thioamide **3**, which was isolated and shown to be the reactive species in these reactions.[20d] Hydroxylamine hydrochloride, being an ambident nucleophile, has been shown to exist in neutral media at pH = 7 in the NH_2OH form, in which the nitrogen centre is softer as well as more nucleophilic in nature than the oxygen centre. Next, β-oxo thioamide **3**, behaving as a 1,3-dielectrophilic synthon, readily undergoes nucleophilic attack by the NH_2 group of the heterobinucleophile NH_2OH preferentially at the soft electrophilic centre of the intermediate β-oxo thioamide **3**, in agreement with the hard and soft (Lewis) acid and base (HSAB) principle,[24] followed by cyclization with the oxo functionality and subsequent dehydration via intermediate **4′** to form the 5-substituted 3-aminoisoxazoles **4**.



Scheme 4. Mechanism for the formation of 5-substituted 3-aminoisoxazoles **4**.

Conclusions

We have developed an efficient and highly regioselective one-pot three-component synthesis of 5-substituted 3-aminoisoxazoles from β-oxo dithioesters with a wide range of diversity at the 3- and 5-positions. By using this new protocol, a small library (32 compounds) of hitherto unreported and synthetically demanding 5-substituted 3-aminoisoxazoles has been achieved, which is useful for the parallel synthesis of libraries of isoxazole analogues. The mechanism of the reaction has been established experimentally by the isolation of a thioamide intermediate and shown to be in agreement with HSAB theory.

Experimental Section

General: All reagents were commercial and purchased from Merck, Aldrich and Fluka, and were used as received. Solvent ethanol was dried and distilled according to a conventional procedure. β-Oxo dithioesters were prepared according to a known procedure.[21a,21b] ^1H and ^{13}C NMR spectra were recorded with a JEOL AL 300 FT-NMR spectrometer. Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Varian 3100 FT-IR spectrophotometer. Electrospray ionisation mass spectra were recorded with a Waters-Q-Tof Premier-HAB213 instrument. XRD data were measured with an Xcalibur Oxford CCD diffractometer. All the reactions were monitored by TLC on precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light for visualization. Melting points were determined with a Buchi B-540 melting point apparatus and are uncorrected.

General Method for the Synthesis of 3-Alkyl/Arylamino-5-alkyl/arylisoxazoles 4: β-Oxo dithioester **1** (1.0 mmol) was added to dry ethanol (5 mL) in a 25 mL round-bottomed flask. Cyclic secondary/primary alkyl/arylamine **2** (1.2 mmol) was added, and the reaction mixture was heated at reflux for 1–10 h. When β-oxo dithioester **1** had been fully converted into the corresponding β-oxo dithiamide **3** (reaction monitored by TLC), hydroxylamine (4.0 mmol; generated from 4.0 mmol of $NH_2OH{\cdot}HCl$ and 4.0 mmol KOH in 2 mL of water) was added to the reaction mixture, which was heated at reflux for a further 2–4 h. The ethanol was removed under vacuum, and water (20 mL) was added to the residue. Then the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The crude reaction mixture was purified by column chromatography using a mixture of ethyl acetate/*n*-hexane in an appropriate ratio as determined by TLC analysis.

5-(4-Chlorophenyl)-3-(morpholin-4-yl)isoxazole (4ac): White solid. M.p. 168–169 °C. IR (KBr): $\tilde{\nu}$ = 1629, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (t, J = 6.9 Hz, 2 H), 7.42 (t, J = 9.6 Hz, 2 H), 6.15 (s, 1 H), 3.83 (t, J = 4.5 Hz, 4 H), 3.32 (t, J = 4.8 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 167.5, 136.0, 129.1, 128.9, 127.8, 126.8, 126.1, 90.3, 66.2, 65.9, 47.4, 46.6 ppm. HRMS: calcd. for $[M + H]^+$ 265.0738; found 265.0742.

5-Phenyl-3-(4-phenylpiperazinyl)isoxazole (4ba): White solid. M.p. 200–201 °C. IR (KBr): $\tilde{\nu}$ = 1625, 1595, 1545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.72 (m, 2 H), 7.44–7.42 (m, 3 H), 7.32–7.26 (m, 3 H), 6.99–6.88 (m, 2 H), 6.21 (s, 1 H), 3.51 (t, J = 4.5 Hz, 4 H), 3.27 (t, J = 5.1 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 167.4, 151.2, 130.0, 129.2, 128.8, 127.8, 125.6, 120.4, 116.6, 90.3, 48.9, 47.4 ppm. HRMS: calcd. for $[M + H]^+$ 306.1601; found 306.1609.

5-(4-Chlorophenyl)-3-(phenylamino)isoxazole (4gc): White solid. M.p. 180–181 °C. IR (KBr): $\tilde{\nu}$ = 3386, 2921, 1738, 1625, 1555 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.1 Hz, 2 H), 7.44 (d, J = 8.1 Hz, 2 H), 7.37–7.32 (m, 4 H), 7.02 (br. s, 1 H), 6.30 (s, 1 H), 6.21 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 161.5, 140.4, 136.2, 129.3, 129.2, 126.9, 125.9, 122.0, 117.7, 92.2 ppm. HRMS: calcd. for $[M + H]^+$ 271.0633; found 271.0634.

Supporting Information (see footnote on the first page of this article): Synthetic procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra of all the final compounds.

Acknowledgments

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