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Development of methodologies for the regioselective synthesis of four series of regioisomer isoxazoles from β-enamino diketones†

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Four methodologies are reported for the regioselective synthesis of four series of regioisomer isoxazoles from cyclocondensation of β-enamino diketones and hydroxylamine hydrochloride. Regiochemical control was achieved by varying reaction conditions and substrate structure. The mild reaction conditions used to access 4,5-disubstituted, 3,4-disubtituted, and 3,4,5-trisubstituted regioisomer isoxazoles, as well as the pharmacological and synthetic potential of the products, make these novel methodologies very powerful.

Introduction

The isoxazole is an important framework because it is the core structure of remarkable medicinal products.[1] For example, parecoxib (anti-inflammatory); sulfamethoxazole (antibiotic); leflunomide (antirheumatic); isocarboxazid (antidepressant); and risperidone (antipsychotic) (Fig. 1). Moreover, isoxazoles are masked 1,3-dicarbonyl equivalents,[2] which serve as precursors for natural product synthesis, as for example tetracycline antibiotics.[2c–h] For this reason, many synthetic methods have been reported for the synthesis of functionalized isoxazoles,[3] including ring construction with functionalized precursors by 1,3-dipolar cycloadditions[4] or cyclocondensation[5] reactions. One of the most popular, oldest, and most important methods for the synthesis of isoxazoles is cyclocondensation of 1,3-dicarbonyl with hydroxylamine (Claisen isoxazole synthesis).[5a–i] However, this approach suffers from frequent formation of a regioisomeric mixture of isoxazoles with poor selectivity, harsh reaction conditions, and a limited reaction scope. Furthermore, obtaining 4-substituted isoxazoles using this approach has been challenging. However, development of new cyclocondensation reactions has received little attention. Despite these challenges, our research group was motivated to develop a new methodology for synthesis of functionalized isoxazoles from β-enamino diketone and hydroxylamine. The β-enamino diketones have been employed as precursors in functionalized heterocycles synthesis due to their excellent 1,3-dielectrophilic system, and in general they allow better control of regioselectivity.[6]

Over time, we have developed regioselective synthetic methodologies for the synthesis of multifunctionalized heterocycles from β-enamino diketones and different dinucleophiles.[6] Variations in reaction conditions,[6e] Lewis acid,[6f] and β-enamino diketone structure[6e,f] have resulted in regiochemical control of pyrazoles,[6a–c,e,f] pyrazolo-pyridazinones,[6b,c] pyrimidines,[6d] and their derivatives. Thus, we believe that the enamino diketones are potential precursors for the regioselective synthesis of functionalized isoxazoles by cyclocondensation with hydroxylamine. To our knowledge, there is only a single report in the literature regarding isoxazole synthesis from enamino diketone and hydroxylamine, where the authors have used a symmetrical β-enamino diketone.[7]

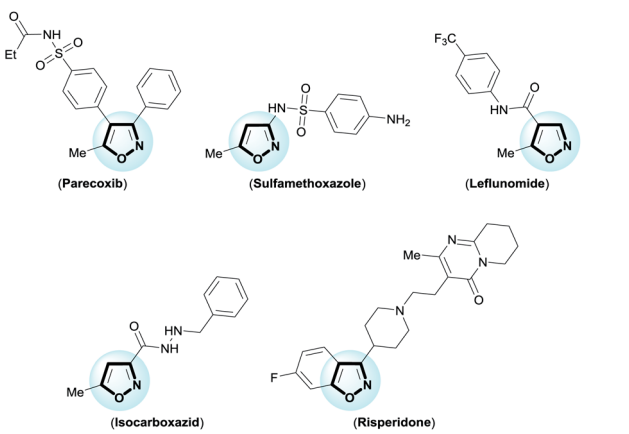

Fig. 1 Examples of medicinal products with the isoxazole moiety.

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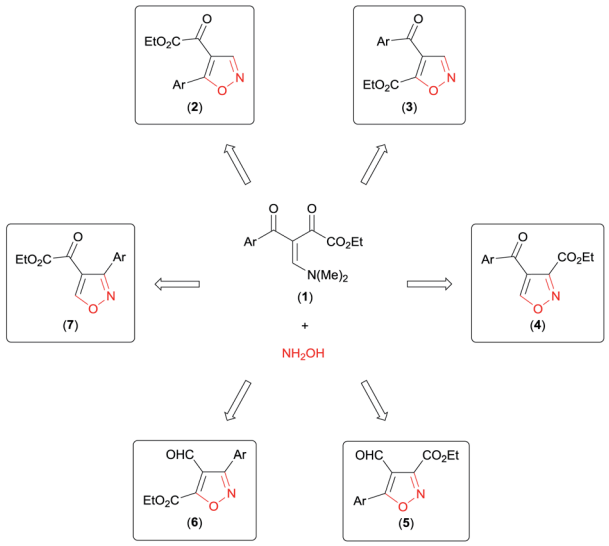
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all compounds, copies of NMR spectra, and crystallographic data. CCDC [CCDC-1589617 (**2a**), CCDC-1589618 (**3a**), CCDC-1589619 (**4a**), CCDC-1589620 (**5a**)]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra13343j



Scheme 1 Possible regioisomer isoxazoles obtained by cyclocondensation of β-enamino diketone with hydroxylamine.

Furthermore, a study of reactivity of the β-enamino diketone system with hydroxylamine has not yet been reported.

Analysing the reactive potential of the β-enamino diketone precursor in the cyclocondensation reaction with hydroxylamine, we observed that it would lead to formation of six regioisomer isoxazoles (Scheme 1). Thus, continuing our interest in this area, we report herein four methodologies to obtain functionalized 4,5-disubstituted isoxazoles, 3,4-disubstituted isoxazoles, and 3,4,5-trisubstituted isoxazoles by regiochemical control of the cyclocondensation reaction of β-enamino diketones with hydroxylamine.

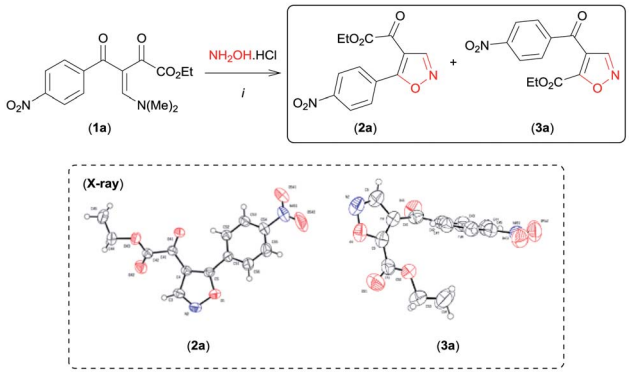
Results and discussion

We began this study using the β-enamino diketone **1a**[8] and hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) as model substrates (Table 1). Gratifyingly, in EtOH at room temperature, these substrates performed well, leading to a regioisomeric mixture of the 4,5-disubstituted isoxazoles **2a** and **3a** with selectivity favouring **3a** in good yield (Table 1, entry 1). The structure of **2a** and **3a** were established by NMR spectral data and unambiguously confirmed by X-ray crystallography[9a,b] (see Fig. SI 1 and 2 for full details, ESI†). Encouraged by these results, other reaction conditions were investigated (Table 1). First, based on data recently reported by Souza *et al.*,[6e] we examined MeCN and the mixture H_2O/EtOH (1 : 1) as solvents in the reaction of **1a** with $NH_2OH \cdot HCl$ (Table 1, entries 2 and 3). The use of the aprotic polar solvent MeCN resulted in **2a** as the main product in good yield (Table 1, entry 2).

On the other hand, the protic polar solvents mixture H_2O/EtOH yielded **3a** as the main product (Table 1, entry 3), but this solvent was found to be less regioselective than EtOH (Table 1, entry 1). Next, we examined the reaction mediated by bases at room temperature (Table 1, entries 4–7, 10 and 11). Interestingly, only pyridine was compatible with the reaction, favouring the regioselective formation of **2a** in EtOH and mainly in MeCN (Table 1, entries 4 and 5). The reactions of other bases led to the formation of **2a** and **3a** as intractable mixtures of several products (Table 1, entries 6 and 7). Finally, by reacting **1a** with $NH_2OH \cdot HCl$ in EtOH at reflux, **3a** was formed with higher regioselectivity (Table 1, entry 8) than at room temperature (Table 1, entry 1). In contrast, varying the reaction temperature in MeCN we discovered that increasing the temperature can jeopardize the regioselectivity of the reaction (Table 1, entry 9). In general, regioisomer **2a** was favoured in MeCN with pyridine at room temperature (Table 1, entry 5), whereas **3a** was preferentially formed in EtOH at reflux (Table 1, entry 8).

Having established the reaction conditions for synthesis of both regioisomeric 4,5-disubstituted isoxazoles **2a** and **3a** with moderate regioselectivity, we became interested in reversing the reactivity of the β-enamino diketone **1a** toward hydroxylamine hydrochloride by varying the reaction conditions, so as to access 3,4-disubstituted isoxazoles regioselectively. To our surprise, when **1a** was reacted with $NH_2OH \cdot HCl$ in the presence of the Lewis acid carbonyl activator BF_3 ($BF_3 \cdot OEt_2$) (0.5 equiv.) in MeCN at room temperature, the desired 3,4-disubstituted isoxazole **4a** was formed as the main product (Table 2, entry 1). The

Table 1 Optimization of reaction conditions of **1a** with $NH_2OH \cdot HCl$ to access 4,5-disubstituted isoxazoles regioisomers **2a** and **3a** regioselectively[a]



	i			Ratio[b] (%)		
Entry	Solvent	Base	Time (h)/Temp. (°C)	**2a**	**3a**	Yield[c] (%)
1	EtOH	—	10/25	35	65	73
2	MeCN	—	16/25	65	35	81
3	EtOH/H_2O	—	10/25	40	60	68
4	EtOH	Py	2/25	64	36	71
5	**MeCN**	**Py**	**2/25**	**76**	**24**	**87**
6	MeCN	DBU	2/25	—[d]		—
7	MeCN	K_2CO_3	2/25	—[d]		—
8	**EtOH**	—	**1/reflux**	**23**	**77**	**76**
9	MeCN	—	3/reflux	54	46	78
10	MeCN	Py	1/reflux	45	55	80
11	EtOH	Py	1/reflux	62	38	74

[a] Reaction conditions: **1a** (0.5 mmol), $NH_2OH \cdot HCl$ (0.6 mmol, 1.2 equiv.), base (0.6 mmol, 1.2 equiv.), solvent (4 mL). [b] Calculated from the ^{1}H-NMR spectrum of crude product. [c] Isolated yield (regioisomeric mixture). [d] **2a** and **3a** as intractable mixtures of several products.

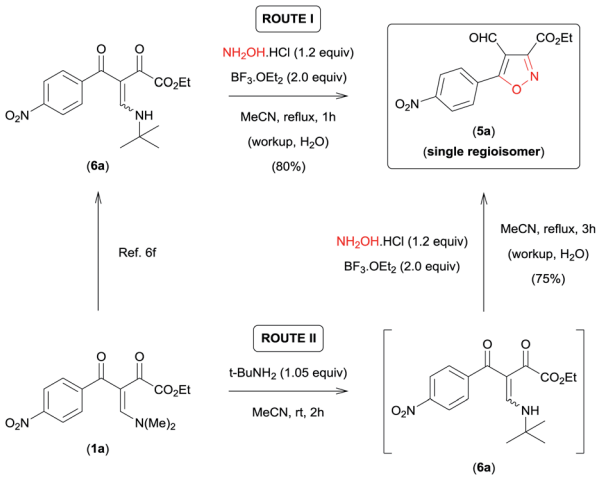
structure of **4a** was unambiguously established from its spectral and X-ray crystallographic data[9c] (see Fig. SI 3 for full details, ESI†).

By optimization of reaction conditions using this protocol, we observed that regioselectivity for the formation of isoxazole **4a** was dependent on the amount of BF_3 (Table 2, entries 1–4) and the solvent used (Table 2, entries 5 and 6). We obtained **4a** with high regioselectivity (90%) in good yield (79%) employing 2 equivalents of BF_3 in MeCN with pyridine at room temperature (Table 2, entry 5). The by-product mixed with **4a** under these conditions (Table 2, entry 5) was isolated and characterized as 3,5-disubstituted 4-formyl-isoxazole **5a** based on NMR spectral analysis and single crystal X-ray analysis[9d] (see Fig. SI 4 for full details, ESI†).

On the basis of these observations, we have devoted our efforts to developing a methodology which allows to access **5a** regioselectively. According to the data recently reported by da Silva *et al.*,[6f] the presence of an aminoalkyl secondary group with high steric demand (i-PrNH– or *t*-BuNH–) bound to the β-carbon of the β-enamino diketone system in combination with the Lewis acid carbonyl activator BF_3 provides conditions for the regiocontrolled reaction of β-enamino diketones with aryl hydrazines to give 3,5-disubstituted 4-formyl-*N*-arylpyrazoles with high regioselectivity. Thus, we tested the viability of this approach for the regioselective preparation of 3,5-disubstituted 4-formyl-isoxazole **5a**. When we tested the reaction of β-enamino diketone **6a** (ref. 6*f*) (1.0 equiv.), prepared from **1a** (ref. 8) (Scheme 2), with $NH_2OH{\cdot}HCl$ (1.2 equiv.) in MeCN and $BF_3{\cdot}OEt_2$ (2.0 equiv.) at reflux for 1 h, the desired isoxazole **5a** was obtained with 100% regioselectivity and in good yield (80%) (Scheme 2, ROUTE I).

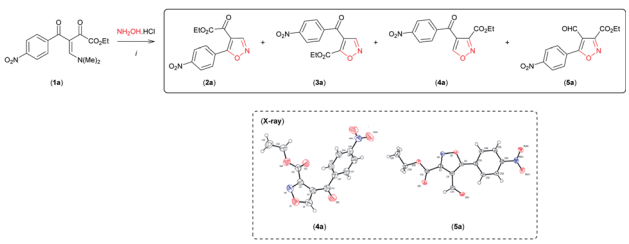
Subsequently, the efficiency of this protocol was further improved by developing a sequential one-pot procedure to obtain isoxazole **5a** directly from the β-enamino diketone **1a** (Scheme 2, ROUTE II). The best results for this procedure were obtained by *in situ* generation of the β-enamino diketone precursor **6a** from treatment of **1a** with *tert*-butylamine (1.05 equiv.) in MeCN at room temperature for 2 h, followed by the addition of $NH_2OH{\cdot}HCl$ (1.2 equiv.) and $BF_3{\cdot}OEt_2$ (2.0 equiv.) under reflux of MeCN for 3 h (Scheme 2, ROUTE II). Through this procedure **5a** was also obtained with 100% regioselectivity and a similar yield when prepared directly from the β-enamino diketone precursor **6a** (Scheme 2, ROUTE I).

Having in hand the optimal reaction conditions to access 4,5-disubstituted (regioisomers **2a** and **3a**, Table 1, entries 5 and



Scheme 2 ROUTE I – Synthesis of 3,5-disubstituted 4-formyl-isoxazol **5a** from β-enamino diketone **6a**; ROUTE II – sequential one-pot procedure to obtain **5a** from β-enamino diketone **1a**.

Table 2 Optimization of reaction conditions of **1a** with $NH_2OH{\cdot}HCl$ mediated by $BF_3{\cdot}OEt_2$ to access 3,4-disubstituted isoxazole **4a** regioselectively[a]



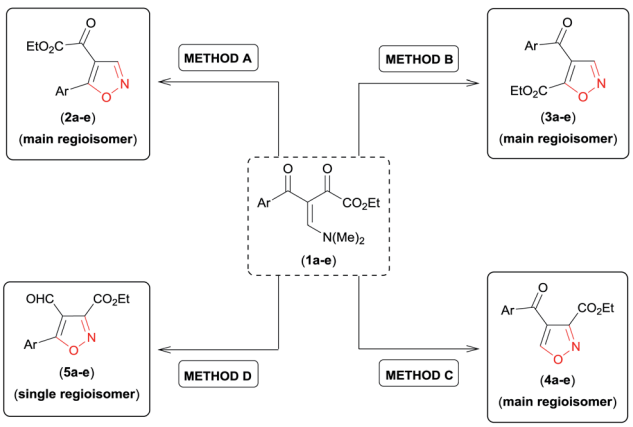
	i			Ratio[b] (%)				
Entry	Solvent	$BF_3{\cdot}OEt_2$ (equiv.)	Time (h)	**2a**	**3a**	**4a**	**5a**	Yield[c] (%)
1	MeCN	0.5	18	37	13	50	—	—
2	MeCN	1.0	20	22	8	70	—	—
3	MeCN	1.5	24	9	—	81	10	—
4	MeCN	2.0	24	—	—	90	10	79
5[d]	**MeCN**	**2.0**	**5**	—	—	**90**	**10**	**79**
6[d]	EtOH	2.0	2	64	36	—	—	—

[a] Reaction conditions: **1a** (0.5 mmol), $NH_2OH{\cdot}HCl$ (0.6 mmol, 1.2 equiv.), room temperature, solvent (4 mL). [b] Calculated from the ^{1}H-NMR spectrum of crude product. [c] Isolated yield (regioisomeric mixture). [d] Pyridine (1.4 equiv.).

8, respectively), 3,4-disubstituted (regioisomer **4a**, Table 2, entry 5), and 3,5-disubstituted 4-formyl (regioisomer **5a**, Scheme 2, ROUTE II) isoxazoles regioselectively from β-enamino diketone **1a** and $NH_2OH{\cdot}HCl$, we examined the scope of this reaction under the conditions reported above, varying the electronic properties of the β-enamino diketone substrate **1**. The results are summarized in Table 3.

Similar to the β-enamino diketone substrate **1a** (Table 3, entries 1, 6, 11 and 16), all substrates examined (**1b–e**) were found to undergo the desired transformation to give the corresponding products in good to excellent yields (62–90%) (Table 3, entries 2–5, 7–10, 12–15, and 17–20). In general, the electronic nature of the Ar substituent on the β-enamino diketone **1a–e** imposed a small effect on the regioselectivity of the reaction for methods A and B. For method A, the substrate bearing the stronger *p*-OMe (**1e**) electron-donating substituent provided low regioselectivity for the formation of the isoxazole regioisomer **2** (Table 3, entry 5), while the *p*-NO_2 electron-withdrawing substituent provided high regioselectivity (Table 3, entry 1). For the other substituents (Table 3, entries 2–4), regioisomer **2** was obtained with moderate regioselectivity. On the other hand, for method B we did not see a clear correlation of the electronic nature of the substituents (Ar) with the regioselectivity of the formation of isoxazole **3** (Table 3, entries 6–10). In contrast, regardless of the different electronic properties of the Ar substituent on β-enamino diketone **1a–e**, isoxazoles regioisomer **4** and **5** were always obtained with high regioselectivity (Table 3, entries 11–20).

Table 3 Substrate scope[a]



METHOD A: NH_2OH.HCl (1.2 equiv), Py (1.2 equiv), MeCN, rt, 2h.
METHOD B: NH_2OH.HCl (1.2 equiv), EtOH, reflux, 1h.
METHOD C: NH_2OH.HCl (1.2 equiv), Py (1.4 equiv), $BF_3.OEt_2$ (2.0 equiv), MeCN, rt, 5h.
METHOD D: **(1)** t-BuNH_2 (1.05 equiv), MeCN, rt, 2h;
(2) NH_2OH.HCl (1.2 equiv), $BF_3.OEt_2$ (2.0 equiv), MeCN, reflux, 3h.
(3) Workup, H_2O.

Entry	Substrate (Ar)	Method	Ratio[b] (%)	Yield[c] (%)
1	**1a** (4-$NO_2C_6H_4$)	A	**2a**(76), **3a**(24)	87 (65)
2	**1b** (4-FC_6H_4)	A	**2b**(62), **3b**(38)	88 (53)
3	**1c** (Ph)	A	**2c**(65), **3c**(35)	89 (57)
4	**1d** (4-MeC_6H_4)	A	**2d**(60), **3d**(40)	90 (52)
5	**1e** (4-$OMeC_6H_4$)	A	**2e**(58), **3e**(42)	90 (50)
6	**1a** (4-$NO_2C_6H_4$)	B	**2a**(23), **3a**(77)	76 (58)
7	**1b** (4-FC_6H_4)	B	**2b**(20), **3b**(80)	82 (65)
8	**1c** (Ph)	B	**2c**(20), **3c**(80)	81 (64)
9	**1d** (4-MeC_6H_4)	B	**2d**(20), **3d**(80)	81 (63)
10	**1e** (4-$OMeC_6H_4$)	B	**2e**(35), **3e**(65)	83 (52)
11	**1a** (4-$NO_2C_6H_4$)	C	**4a**(90), **5a**(10)	79 (70)
12	**1b** (4-FC_6H_4)	C	**4b**(90), **5b**(10)	81 (71)
13	**1c** (Ph)	C	**4c**(90), **5c**(10)	72 (64)
14	**1d** (4-MeC_6H_4)	C	**4d**(90), **5d**(10)	73 (65)
15	**1e** (4-$OMeC_6H_4$)	C	**4e**(90), **5e**(10)	83 (74)
16	**1a** (4-$NO_2C_6H_4$)	D	**5a**(100)	(75)
17	**1b** (4-FC_6H_4)	D	**5b**(100)	(65)
18	**1c** (Ph)	D	**5c**(100)	(62)
19	**1d** (4-MeC_6H_4)	D	**5d**(100)	(70)
20	**1e** (4-$OMeC_6H_4$)	D	**5e**(100)	(68)

[a] Reaction conditions: **1b–e** (0.5 mmol), $NH_2OH{\cdot}HCl$ (0.6 mmol, 1.2 equiv.), solvent (4 mL). [b] Calculated from the ^{1}H-NMR spectrum of crude product. [c] Isolated yields (regioisomeric mixture); yields in parentheses are yields of the main regioisomer isolation by column chromatography.

Finally, through detailed analysis of the NMR spectral data of the new isoxazoles reported here, we observed that difference in the chemical shifts of ^{1}H and ^{13}C allow a simple assignment of the different regioisomeric forms obtained. For example, we use isoxazoles **2a**, **3a**, **4a**, and **5a** as a model to show these differences (Fig. 2).

For the disubstituted isoxazoles **2a**, **3a**, and **4a**, the hydrogen atom attached to the isoxazole nucleus (H3 for **2a** and **3a**, H5 for **4a** – Fig. 2) have notable differences in the chemical shifts of ^{1}H NMR spectrum. The H3 atom in **3a** (8.59 ppm) is more shielded than the H5 atom in **4a** (8.89 ppm) by a difference of approximately 0.30 ppm, whereas H5 (**4a**) is more shielded than the H3 atom in **2a** (9.12 ppm) by about 0.23 ppm (Fig. 2). With regard to ^{13}C NMR spectra of disubstituted isoxazoles, the major differences between the chemical shifts of the 4,5 (**2a** and **3a**) and the 3,4 (**4a**)-disubstituted regioisomers are related to the carbon atoms C3 in **2a** and **3a**, and C5 in **4a** (Fig. 2). This is because the C5 atom signal (compound **4a**) is approximately 10 ppm more deshielded than the corresponding atom (C3) in **2a** and **3a** (Fig. 2). For the 4,5-disubstituted regioisomers **2a** and **3a**, the signal of the ketone carbonyl attached at the 4-position of the isoxazole ring shows considerable differences in the chemical shifts of the ^{13}C NMR spectrum, because the ketone carbonyl signal in **2a** is more shielded than the ketone carbonyl in **3a** by

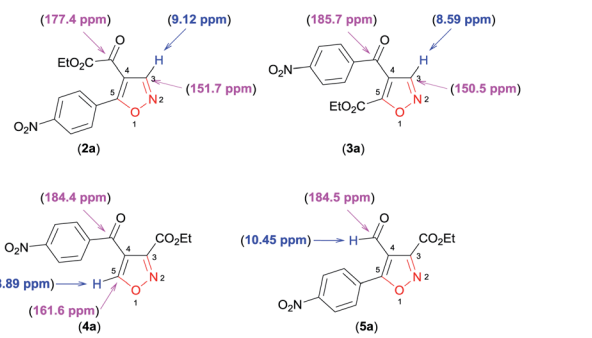


Fig. 2 ^{1}H and ^{13}C NMR chemical shifts of the regioisomers **2a**, **3a**, **4a**, and **5a**.

about 8.3 ppm (Fig. 2). Unambiguously, 3,5-disubstituted 4-formyl isoxazole **5a** could be identified by the characteristic chemical shifts of aldehyde hydrogen and carbon of the ^{1}H and ^{13}C NMR spectra (Fig. 2).

Conclusions

In summary, we have developed four methodologies for the regioselective synthesis of polyfunctionalized isoxazoles by cyclocondensation of β-enamino diketones with hydroxylamine. The regiochemistry of the reaction has been controlled by: the solvent; use of pyridine; the Lewis acid carbonyl activator BF_3; and the structure of the β-enamino diketone. These variations allowed access to four of the six possible regioisomer isoxazoles with good yields, which have different substitution patterns: 3,4-disubstituted, 4,5-disubstituted-, and 3,4,5-trisubstituted isoxazoles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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