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Synthesis of 3,5-disubstituted isoxazoles by domino reductive Nef reaction/cyclization of β-nitroenones†

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β-Nitroenones can be efficiently converted into 3,5-disubstituted isoxazoles by using tin(II)chloride dihydrate and ethyl acetate as a reducing agent and solvent, respectively. Products are obtained in good yields and several functional groups are tolerated thanks to the mild reaction conditions.

Introduction

Isoxazoles constitute one of the most important classes of nitrogen–oxygen containing five-membered heterocyclic systems, as the isoxazole ring is classified as a privileged structure.[1] Indeed, their derivatives exhibit an extensive range of biological activities due to the broad spectrum of protein targets by which the isoxazole compounds could interact.[2] In particular, the anticancer, antibacterial, antimicrobial, antiviral, and antituberculosis activities are just some of the medicinal properties of isoxazole derivatives (Fig. 1).[3] Moreover, the isoxazole scaffold is also a key starting material to access more complex molecular architectures.[4]

Due to their importance, several procedures for synthesizing poly-functionalized isoxazoles are reported in the literature (Scheme 1).[5] The most effective routes are pivoted on 1,3-dipolar cycloaddition reactions of electron-rich alkynes and nitrile oxides, which are generated *in situ* from nitroalkanes **A** or oximes **B**. Although the conversion of **A** into nitrile oxides is quite effective, it usually requires harsh reaction conditions and/or dangerous and toxic reagents such as $POCl_3$, phenyl isocyanate, PPA and DMTMM.[6] On the other hand, **B** can be directly converted into nitrile oxides by oxidizing agents such as hypervalent iodine reagents, NaOCl and Oxone®,[7] or alternatively *via* imidoyl chlorides **C** by a chlorination and base-promoted elimination approach.[8] Despite the efficiency of this synthetic approach, an appropriate regiochemical control in the isoxazole formation is not always achievable using unsymmetrical alkynes. Alternative methods involving intramolecular cyclization of specific structures were also exploited. In this context, α,β-acetylenic oximes **D** are suitable for cyclization into isoxazoles by metal catalysis (*e.g.* $AuCl_3$, CuCl, $Pd(OAc)_2$).[9] Similarly dinitro compounds **E** are easily converted into the isoxazole core under mild basic conditions; nonetheless, R and R^1 must be identical in order to prevent the formation of regioisomeric products.[10] Finally, 1,3-dielectrophiles **F** can be used as starting materials for functionalized isoxazoles; nevertheless, even in this case an appropriate selection of the starting scaffold is crucial to prevent regioisomeric issues.[8,11]

β-Nitroenones are a subclass of nitroolefins featuring the simultaneous presence of the ketone and nitro group in α- and β-positions to the double bond, respectively (Fig. 2).[12] The presence of both electron-withdrawing groups dramatically enhances the reactivity and the synthetic versatility of β-nitroenones, making them useful precursors of highly functionalized materials and heterocyclic systems.[13]

Following our ongoing research on the chemistry of β-nitroenones **1** and inspired by the pioneering studies by Wieland at the very beginning of the last century, and by Viel

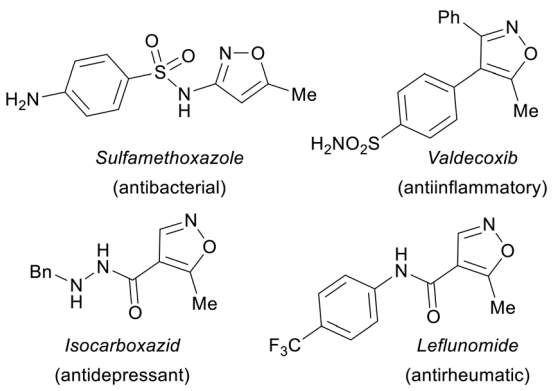

Fig. 1 Examples of biologically active isoxazole derivatives.

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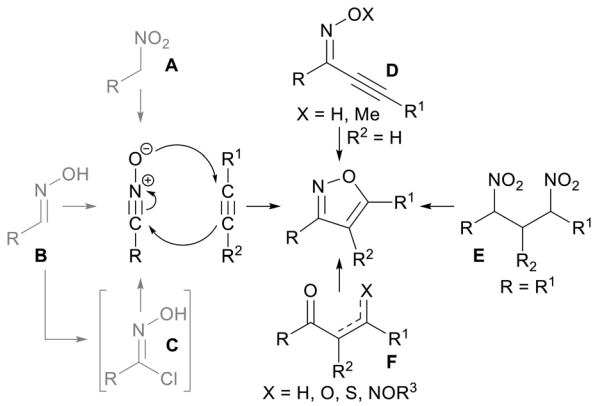


Scheme 1 Main synthetic routes to prepare isoxazoles.

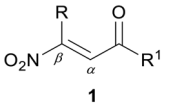
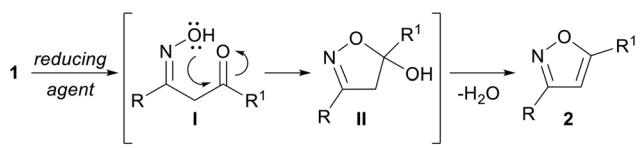


Fig. 2 General structure of β-nitroenones.

in 1979 (limited to α-acyl β-nitrostilbenes),[14] we have now realized a general and efficient conversion of **1** into 3,5-disubstituted isoxazoles **2**. The protocol is based on the preliminary reductive Nef reaction of the nitroalkene **1** to the corresponding oxime **I**,[15] which intramolecularly reacts with the carbonyl function generating the five-membered ring **II**, which upon dehydration finally affords the isoxazole system **2** (Scheme 2).

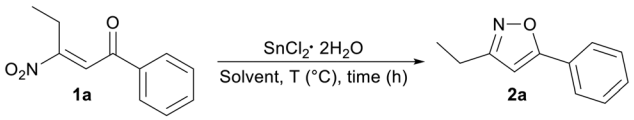
Results and discussion

To find the best reaction conditions, we profiled the conversion of **1a** into **2a** in terms of solvent, temperature, reaction time, stoichiometry and reducing species (Table 1). In particular, the known ability of tin(II) chloride dihydrate to convert nitroalkenes into oximes[16] prompted us to test the reaction using 2 equivalents of this salt in different solvents at room temperature (entries a–e). The reaction was completely ineffective when using dichloromethane (DCM) and toluene, while moderate yields of **2a** were obtained in dioxane, 2-methyltetrahydrofuran (2-MeTHF) and ethyl acetate. Having identified 2-MeTHF and EtOAc as the most promising solvents for the reaction, we screened different reaction temperatures.



Scheme 2 Probable reaction mechanism.

Table 1 Optimization studies



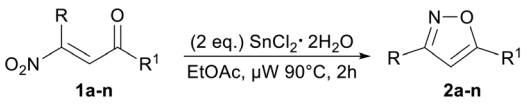
Entry	Solvent	Temp. (°C)	Time (h)	Yield[f] (%) of **2a**
a	2-MeTHF	r.t.[a]	8	34 + **1a**
b	Dioxane	r.t.[a]	8	8 + **1a**
c	DCM	r.t.[a]	8	**1a**
d	Toluene	r.t.[a]	8	**1a**
e	EtOAc	r.t.[a]	8	32 + **1a**
f	2-MeTHF	50[a]	8	42 + **1a**
g	2-MeTHF	Reflux[a]	2	69
h	2-MeTHF	90 °C[a,b]	2	74
i	EtOAc	50[a]	8	44 + **1a**
j	EtOAc	Reflux[a]	2	70
k	EtOAc	90 °C[a,b]	2	79
l	EtOAc	90 °C[a,c]	2	73
m	EtOAc	90 °C[b,d]	2	50
n	EtOAc	90 °C[b,e]	2	77

[a] Reaction performed in the presence of 2 eq. of $SnCl_2 \cdot 2H_2O$. [b] Reaction performed under microwave conditions. [c] Reaction performed in a sealed vial using a conventional sand bath heater. [d] Reaction performed in the presence of 1.5 eq. of $SnCl_2 \cdot 2H_2O$. [e] Reaction performed in the presence of 2.5 eq. of $SnCl_2 \cdot 2H_2O$. [f] Yield of the pure isolated product.

At 50 °C, we recorded similar results compared to that when conducting the reaction at room temperature, and in fact **2a** was obtained just in a slightly better yield (entries f and i). Successively, we increased the reaction temperature to reflux conditions, observing for both reactions the complete consumption of **1a** over two hours and isolating **2a** in 69% and 70% yields, respectively (b.p.: 2-MeTHF = ~80 °C; EtOAc = ~77 °C; entries g and j). Finally, by means of a Biotage® Initiator microwave synthesizer, we further increased the temperature to 90 °C. Under these conditions, we attained a cleaner reaction mixture and higher yields, and particularly the best yield (79%) was observed when conducting the reaction in EtOAc (entries f–k). This result probably depends on the more efficient energy transfer occurring under microwave irradiation than with the conventional heating technique.[17] In this regard, we repeated the reaction at 90 °C in a sealed vial and by means of a sand bath heater; however, **2a** was isolated in a lower yield (entry l). It is important to note that the lowering of the amount of tin(II) chloride dihydrate from 2.0 to 1.5 equivalents leads to a significant decrease of the yield, while an increase up to 2.5 equivalents does not improve the yield (entries m and n). Finally, the conversion of **1a** into **2a** was also attempted using $FeCl_3$, $FeCl_2 \cdot 4H_2O$, CuCl and $CrCl_2$ under the optimized reaction conditions; nevertheless, only chromium(II) chloride led to the isolation of **2a**, albeit in a very poor yield (8%).

In order to demonstrate the generality of our protocol we tested the optimized reaction conditions with a number of

Table 2 Substrate scope demonstration



R	R^1	Isoxazole **2**	Yield[a] (%)
Et	Ph	**2a**	79, 84[b]
$MeOOC(CH_2)_5$	Ph	**2b**	55, 68[b]
$CH_3(CH_2)_6$	3-MeO–C_6H_4	**2c**	80, 86[b]
$AcO(CH_2)_3$	4-MeO–C_6H_4	**2d**	85
$CH_2{=}CH(CH_2)_4$	2-Thienyl	**2e**	78
$CH{\equiv}C(CH_2)_3$	2-Thienyl	**2f**	79
$CH_3(CH_2)_6$	2-Naphthyl	**2g**	83
$CH_2{=}CH(CH_2)_3$	2-Naphthyl	**2h**	91
$PhCH_2CH_2$	2-Naphthyl	**2i**	72
$Cl(CH_2)_4$	4-Me–C_6H_4	**2j**	82
$CH_3(CH_2)_4$	4-Me–C_6H_4	**2k**	85
Et	3-(*N*-Methylindolyl)	**2l**	84
Ph	4-MeO–C_6H_4	**2m**	79
$CH_3(CH_2)_4$	*t*-Bu	**2n**	62

[a] Yield of the pure isolated product. [b] Reaction performed under flow chemical conditions.

β-nitroenones **1a–n**. In all cases, the target isoxazoles **2a–n** were obtained in good to very good yields (55–91%). Moreover, thanks to the mildness of the reaction conditions, a good variety of functionalities, such as chlorine, ester, thiophene, ether, and double and triple bonds, can be embedded in the substrate (Table 2).

Finally, with the aim of automating the process, we investigated the conversion of β-nitroenones **1a–c** under flow chemical conditions by means of a FlowLab™ system of Uniqsis.[18] The equipment consists of two HPLC pumps, two reservoirs respectively filled with the ethyl acetate solutions of β-nitroenones **1** (reservoir A) and $SnCl_2{\cdot}2H_2O$ (reservoir B), a T-connector **T**, a heated reactor station equipped with a 10 mL PTFE coil reactor **R** and a back pressure regulator (BPR) set at 40 psi (Fig. 3).

Applying the batch optimized reaction conditions to the flow chemical approach (90 °C and 2 hours as residence time), the target isoxazoles **2a–c** were isolated in higher yields than in batch, presumably due to the superior efficiency in the mass and energy exchanges of the flow approach with respect to the batch one.[19]

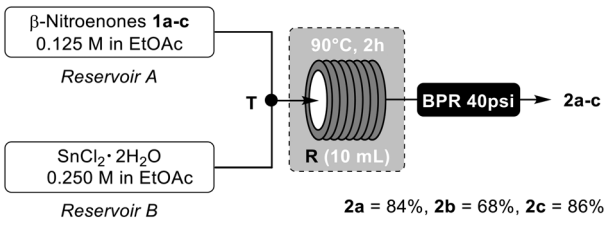


Fig. 3 Scheme of the flow chemical equipment.

Conclusions

In conclusion, we have further demonstrated the usefulness of β-nitroenones as key precursors of privileged structures in medicinal chemistry. In particular, herein we developed a new general and simple protocol for converting β-nitroenones into 3,5-disubstituted isoxazoles under microwave conditions. The protocol allows the preparation of the title compounds in very good yields, under mild reaction conditions compatible with different functional groups. Moreover, the extension of our methodology to flow chemical conditions enables yield improvement and easy process-automation.

Experimental

General remarks

^1H NMR analyses were performed at 400 MHz on a Varian Mercury Plus 400. ^{13}C NMR analyses were carried out at 100 MHz. IR spectra were recorded with a PerkinElmer FTIR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fison Instruments. GS-MS analyses were carried out on a Hewlett-Packard GC/MS 6890 N that works with the EI technique (70 eV). Flow chemical reactions were performed by means of a FlowLab™ system of Uniqsis. Microwave irradiation was performed by means of a Biotage® Initiator. Compounds **1a–n** were prepared starting from alkyl- and arylglyoxals and nitro compounds by following reported procedures.[20]

Batch general procedure

A solution of the appropriate β-nitroenone **1a–n** (1 mmol) and tin(II) chloride dihydrate (2 mmol) in ethyl acetate (13 mL) was irradiated, by means of a Biotage® Initiator microwave oven, at 90 °C for 2 hours. Then, the solution was transferred into a separatory funnel, treated with a 0.5 N aqueous solution of HCl (30 mL), extracted with fresh EtOAc (3 × 30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, after the filtration of sodium sulphate and the evaporation of the solvent under reduced pressure, the crude reaction product **2a–n** was purified by flash column chromatography (hexane : EtOAc = 95 : 5).

Flow general procedure

The appropriate β-nitroenone **1a–c** (1 mmol) was taken up in ethyl acetate (6.5 mL) and placed in reservoir A, and tin(II) chloride dihydrate (2 mmol) was taken up in ethyl acetate (6.5 mL) and placed in reservoir B. The two solutions were simultaneously pumped with a flow rate of 0.042 mL min^{-1} for each pump into a T-connector before passing through a 10 mL PTFE coil reactor heated at 90 °C (residence time 2 hours), and the outflow was dropped into a flask containing 30 mL of a stirring 0.5 N aqueous solution of HCl. The two layers were separated, the aqueous one was extracted with fresh EtOAc (3 × 30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, after the filtration of sodium sulphate

and the evaporation of the solvent under reduced pressure, the crude reaction product **2a–c** was purified by flash column chromatography (hexane : EtOAc = 95 : 5).

Author contributions

A. P. and M. P. conceived the idea and designed the experiments. M. E. I. K. performed the optimization studies. M. E. I. K. and T. L. C. performed the substrate scope analysis and mechanistic studies. A. P. and M. P. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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