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COMMUNICATION

Eco-friendly synthesis of β -nitro ketones from conjugated enones: an important improvement of the Miyakoshi procedure†Serena Gabrielli,^a Alessandro Palmieri,^a Alvise Perosa,^b Maurizio Selva^b and Roberto Ballini^{*a}

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A variety of α,β -unsaturated ketones can be easily converted, at room temperature, into β -nitro ketones by nitration with solid supported nitrite (SSN) and in the presence of acetic acid and cyclopentyl methyl ether.

Nitroalkanes are one of the most fundamental classes of substrates in organic chemistry.¹ This is mainly due to the fact that (i) they allow the easy formation of new carbon–carbon and carbon–heteroatom bonds under very mild reaction conditions,^{2,3} (ii) the nitro group can be converted into a plethora of other functionalities,⁴ and (iii) they are the key starting material for the preparation of a variety of fine chemicals.⁵

Thus, the easy accessibility to nitroalkanes remains an important goal, especially for those functionalized ones.⁶ In this context, of great interest are the β -nitro ketones **1** because these kind of derivatives, or their protected ones, have been demonstrated to be important building blocks in organic synthesis.⁷ These molecules can be obtained (Fig. 1) from three different sources: (i) by halo-nitro displacement of β -halocarbonyl derivatives **2** (way a),^{8a} (ii) via C,C-cross-coupling of nitroalkanes **3** and their silyl derivatives **4** (Ioffe procedure, way b),^{8b} or (iii) by the historical Miyakoshi procedure^{8c} that involves the nitration of conjugated enones **5** using sodium nitrite and acetic acid, in THF as solvent (way c). Although each of the above methods gives access to different interesting molecular structures, way c remains the most used one.

Above all, the Miyakoshi procedure shows important drawbacks because it seems to be limited just to α,β -unsaturated ketones having simple molecular frames, gives moderate yields, needs the presence of organic volatile solvents such as THF⁹ and, moreover, the methodology requires a tedious and non eco-sustainable work-up. Thus, in order to avoid the above limitations, new improvements of this classical method for the preparation of the title compounds would be encouraged.

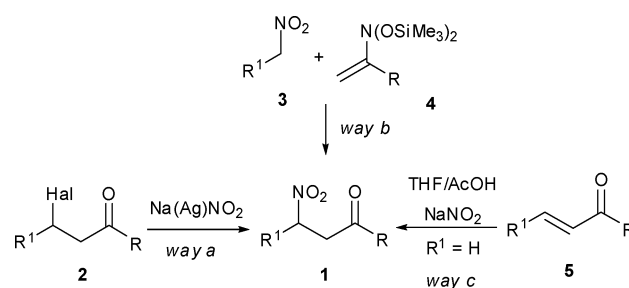


Fig. 1 Main synthetic pathways for the synthesis of β -nitro ketones **1**.

In the course of the last few years, solid supported reagents (SSR) have attracted growing interest since they have demonstrated a great versatility as powerful promoters in a wide number of reactions,¹⁰ increasing the chemical reactivity and simplifying the classical work-up step into an easy filtration, with the consequent minimization of the use of solvents.¹¹ On the other hand, recently, it has been demonstrated that reactions conducted in cyclopentyl methyl ether (CPME), as a new emerging “green solvent”, in contrast to tetrahydrofuran, are comparatively more favourable in terms of eco-sustainability and efficiency, and with consequent reduction of both exposure and flammability safety problems.¹²

In our laboratory in recent years, we have found that the reactivity and the chemical potentialities of the aliphatic nitro compounds often increase by the use of SSR.¹³ Based on these experiences and following our research projects on the chemistry of aliphatic nitro compounds, we have now developed an improved general procedure for the nitration of conjugated enones, employing solid supported nitrite (SSN).¹⁴ Thus, firstly we tested, as model reaction, the nitration of the compound **5a** checking different amounts of both SSN and acetic acid on a variety of solvents, including CPME.

As reported in Table 1, the best yield (89%) was obtained using 3 equivalents of nitrite on polymer, and 5 equivalents of acetic acid on CPME (entry f).

Encouraged by this excellent result and in order to explore the general applicability of our methodology, we submitted a variety of α,β -unsaturated ketones under the optimized reaction conditions.

As reported in Table 2, the reaction gives important yields (60–89%) with a variety of enones, including furyl and aryl vinyl

^aGreen Chemistry Group, School of Science and Technology, Chemistry Division, University of Camerino, Via S. Agostino 1, 62032, Camerino, Italy. E-mail: roberto.ballini@unicam.it; Fax: +39 0737 402297; Tel: +39 0737 402270

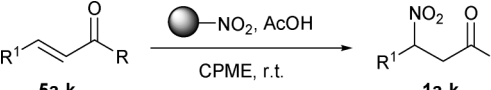
^bDipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari Venezia, Dorsoduro 2137, 30123, Venezia, Italy. E-mail: selva@unive.it; Tel: +39 041 2348687

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Table 1 Optimization studies

Entry	eq. Nitrite on polymer (SSN)	eq. AcOH	Solvent	Yield (%) ^a of 1a
a	1	2	CPME	15
b	1	2	CPME	30
c	2	4	CPME	68
d	3	4	CPME	63
e	4	5	THF	80
f	3	5	CPME	89
g	3	6	CPME	70
h	3	5	EtOAc	55
i	3	5	DCM	65

^a Yield of pure isolated product.**Table 2** Nitration of different unsaturated ketones

				
	5a-k			1a-k
	<i>R</i>	<i>R</i> ¹	Reaction time (h)	Yield (%) ^a of 1
a	Ph(CH ₂) ₂	H	30	89
b	<i>n</i> -C ₈ H ₁₇	H	30	72
c	PhC ₆ H ₄	H	24	82
d	Ph	H	24	86
e	<i>p</i> -MeOC ₆ H ₄	H	30	82
f	<i>p</i> -CF ₃ C ₆ H ₄	H	27	77
g	<i>c</i> -C ₆ H ₁₁	H	30	75
h	2-furyl	H	30	75
i	Cl(CH ₂) ₅	H	30	75
j	Et	H	24	84
k	<i>n</i> -Bu	Me	48	60

^a Yield of pure isolated product.

ketones, independently from the nature of the alkyl group (R) or the presence of other functionalities in the phenyl ring (**1c**, **1e** and **1f**).

However, of particular importance is the success obtained by the nitration of the hindered enone **5k** performed in consistent yield (60%). The latter example is of great importance, because, to the best of our knowledge, it is the first report of the nitration of substituted vinyl ketones, allowing an easy access to secondary nitro compounds, which are difficult to obtain by other methods.

Conclusions

In conclusion, by our method the Miyakoshi procedure has been significantly improved both in terms of efficiency and eco-sustainability. In fact, higher yields have been obtained using a greener solvent (CPME) and the procedure works well even with complex conjugated enones, including substituted vinyl ketones. Furthermore, it is possible to preserve other functionalities, minimizing the work-up step into an easy filtration and evaporation of both solvent and acetic acid, avoiding any classical, tedious aqueous work-up and the use of any drying salts, with the consequent drastic decrease of *E*-factor.

Experimental

General procedure for the synthesis of compounds **1a–k**

Batch reaction was carried out by stirring a mixture of ketone **5** (1 mmol), SSN (3 mmol), acetic acid (5 mmol) and CPME (3 mL). The reaction was allowed to stir for the appropriate time (see Table 2) at room temperature. After the reaction was completed, the resin was filtered off and washed with EtOAc (5 mL), then the solvent was removed under vacuum, and the crude product **1** was purified by flash chromatography column (hexanes : EtOAc = 85 : 15).

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- 14 The nitrite on polymer support (Amberlite®IRA 900 NO₂⁻form) was purchased from Sigma-Aldrich and used directly without any manipulation. The promoter containing ~14% of water and has a loading of ~4 mmol g⁻¹ of NO₂.