Letter

Ytterbium mediated coupling of α-oxonitriles with allylbromides: convenient synthesis of β,γ-unsaturated ketones†

Mukut Gohain,[a] Baikuntha J. Gogoi,[a] Dipak Prajapati*[a] and Jagir S. Sandhu[b]

[a] *Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785 006, Assam, India. E-mail: dr_dprajapati@yahoo.co.uk; Fax: +91 376 2370011*
[b] *Department of Chemistry, Panjabi University, Patiala-147002, India*

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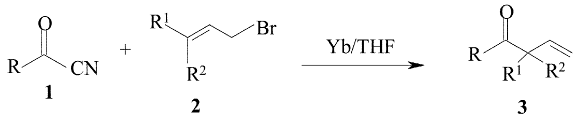
A new and efficient method for the preparation of β,γ-unsaturated ketones has been achieved by the simple reaction of an acyl cyanide with allyl, crotyl and prenyl bromides and ytterbium metal in absolute tetrahydrofuran.

Since Blaise reported the addition of allylic iodide to nitriles, this potentially useful β,γ-unsaturated ketone synthesis has found little attention in organic synthesis.[1] Also, the synthesis of β,γ-unsaturated ketones is complicated, *inter alia*, by a proclivity toward prototropic rearrangements producing conjugated isomeric α,β-unsaturated ketones.[2] Although deconjugation of α,β-unsaturated ketones can be achieved by a variety of methods,[3] mixtures of α,β- and β,γ-unsaturated isomers are often produced. Thus, the reaction conditions need to be as mild as possible. Although a number of synthetic methods are available, only a few have proven useful and practical. Acylation of olefins frequently favours the production of β,γ-unsaturated ketones, but α,β-unsaturated ketones may also be generated.[4] Certain transition-metal-mediated syntheses have been partially successful, but they also suffer from poor regioselectivity.[5] Among other methods, direct oxidation of homoallylic alcohols produced *via* allylboration have been demonstrated to be successful for specific classes.[6] Allylic ketones have also been prepared by the reaction of allylic organometallics of silcon,[7] copper,[8] rhodium,[9] manganese,[10] titanium[11] and mercury[12] with acyl halides, but these reactions have their own merits as well as limitations. In view of the synthetic importance of these ketones, it is desirable to have a general convenient methodology for their synthesis, especially from readily available materials.

In recent years lanthanide metals, lanthanide metal salts and organolanthanide compounds have been widely employed as useful reagents or catalysts in organic synthesis.[13] The pioneering studies by Kagan and co-workers demonstrated the particular effectiveness of ytterbium and samarium as a strong one-electron transfer reducing agents, however, the utilization of ytterbium reagents in synthetic organic chemistry has been comparatively less investigated.[14] We disclose herein the first example of the ytterbium promoted coupling of allylic bromides with a variety of α-oxonitriles to form β,γ-unsaturated ketones in absolute tetrahydrofuran at room temperature. To our knowledge there are no literature reports on the coupling of ketocyanides with allylic halides and this is the first ever report of this kind. It is worth mentioning here that allylindium reagent reacts with a variety of nitriles to give regioselectively the corresponding enamino products[15] but with ytterbium, we did not observe the formation of any such products.

Reaction of benzoyl cyanide **1a** with allylic bromide in the presence of ytterbium metal in dry tetrahydrofuran as the solvent (Scheme 1) produced the corresponding β,γ-unsaturated ketone **3a** in 80% yield. Analysis of the crude mixture did not indicate the formation of any isomeric conjugated α,β-unsaturated ketone as reported by earlier workers.[4a] Similarly, other α-oxonitriles were reacted and the corresponding β,γ-unsaturated ketones were obtained in 70–82% yields. The structures of the β,γ-unsaturated ketones thus obtained were unambiguously identified on the basis of their spectral data (IR, NMR, MS) and finally by comparing with authentic samples. It is worth mentioning here that the reaction time can be reduced from 8 h to 4 h if carried out in refluxing THF, but the yield is less and by-products are formed. The results and scope of this reaction are shown in Table 1. When crotyl bromide was used in place of allyl bromide in the above reaction the corresponding β,γ-unsaturated compound (entry 2) was obtained in 82% yield. In the course of the reaction, substituents such as methoxy, chloro and bromo groups on aromatic rings (entries 4, 5 and 9–11) are not affected under the reaction conditions. Moreover, aromatic nitro compounds, which are known to be reduced by iron carbonyl,[16] coupled with ease with ytterbium to give the corresponding allylic ketone in 75% yield without any reduction of the nitro group.

In order to assess the generality of the process, the reaction was studied with a variety of acyl cyanides. As shown in Table 1, furoyl cyanide reacted with allyl bromide to give the expected allylic ketone (entry 14) but the application of this method to aliphatic acyl cyanide proved unsuccessful and only the decomposition product was isolated (entry 15). It is also noteworthy that the reaction proceeded successfully without the addition of any additives. Moreover, when ytterbium is replaced by inexpensive cadmium powder the coupling proceeded less efficiently and the corresponding allylic ketones were obtained in 50–70% yields. In most cases, the reaction was over within 7–9 h with ytterbium while the reaction takes a little more time with cadmium. Increasing further the reaction time gave no improvement in yield but rather formation of by-products occurred. However, with indium or gallium



$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^1 = R^2 = Me$

Scheme 1

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† Electronic supplementary information (ESI) available: spectral and analytical data for products **3a**–**3n**. See http://www.rsc.org/suppdata/nj/b3/b302491c/

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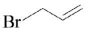
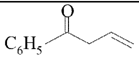
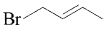
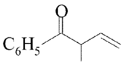
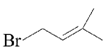
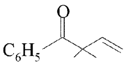
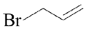
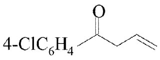
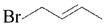
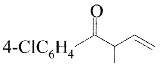
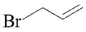
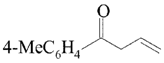
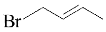
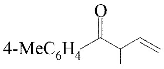
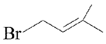
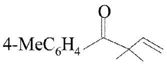
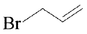
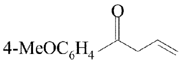
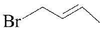
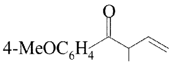
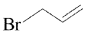
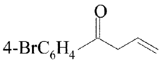
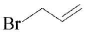
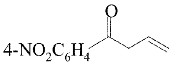
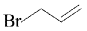
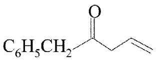
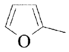
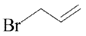
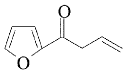
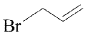
Table 1 Synthesis of β,γ-unsaturated ketones mediated by ytterbium

Entry	Oxonitrile R	Allyl halide **2**	Product **3**		Time/ h	% Yield[a]
1	C_6H_5			**3a**	8	80
2	C_6H_5			**3b**	7	82
3	C_6H_5			**3c**	9	75
4	4-ClC_6H_4			**3d**	8	78
5	4-ClC_6H_4			**3e**	8	75
6	4-MeC_6H_4			**3f**	8	80
7	4-MeC_6H_4			**3g**	9	75
8	4-MeC_6H_4			**3h**	9	70
9	4-$MeOC_6H_4$			**3i**	8	78
10	4-$MeOC_6H_4$			**3j**	8	75
11	4-BrC_6H_4			**3k**	9	70
12	4-$NO_2C_6H_4$			**3l**	9	75
13	$C_6H_5CH_2$			**3m**	9	70
14				**3n**	10	70
15	*n*-C_3H_7		Decomposition products		–	–

[a] All the yields refer to isolated, chromatographically pure compounds.

metal the reaction did not yield any allylic ketone and the starting materials were recovered along with decomposition products, after stirring at room temperature for 18–20 h. Although the detailed mechanism of this reaction is not clear, it is assumed that ytterbium leads to the generation of an active organoytterbium reagent that reacts with the carbonyl group of the oxonitriles to provide the corresponding β,γ-unsaturated ketones. Further studies aimed at expanding the scope of this reaction and understanding its mechanism are in progress.

In conclusion, we have provided a novel and efficient method for the coupling of keto cyanides to form β,γ-unsaturated ketones employing ytterbium in dry THF, which involves a simple work-up and will be a useful and important addition to the existing methodologies. This new procedure has the advantages of using mild reaction conditions, leading to a lack of side products, high yields and above all the method is highly selective.

Experimental

Melting points were taken in open capillary tubes on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded as KBr discs on a Perkin–Elmer 237B IR spectrometer. Microanalyses were performed on a Perkin–Elmer 240C analyser. The ^1H NMR spectra were recorded on a Varian T-60 machine using tetramethylsilane (TMS) as the internal standard. The chemical shifts are recorded as δ values. All the chemicals were purified by distillation or crystallisation prior to use. The 300 MHz NMR spectra were recorded with tetramethylsilane as internal standard (by RSIC, Shillong). Chromatographic purifications was performed with silica gel 60 (120 mesh, Merck).

General procedure for the allylation of α-oxonitriles 1 with allylic bromides 2 in the presence of ytterbium: synthesis of β,γ-unsaturated ketones

In a typical case, ytterbium metal (1.70 g, 10 mmol) was added to a stirred solution of allyl bromide (2.44 g, 20 mmol) in 10 ml of dry tetrahydrofuran and the stirring was continued for 20 min at room temperature. Freshly prepared benzoyl cyanide (1.31 g, 10 mmol) in 5 ml of THF was then added dropwise and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered through celite and the filtrate was evaporated in a rotary evaporator. The residue thus obtained was extracted with diethyl ether (3 × 30 ml). The combined ether extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product, which on further purification by column chromatography on silica gel gave exclusively the corresponding allylic ketone **3a** (entry 1) in 80% yield. There was no evidence for the formation of any isomeric conjugated α,β-unsaturated ketones as reported by earlier workers. Similarly, other α-oxonitriles **1b**–**1n** were reacted and the corresponding β,γ-unsaturated ketones **3b**–**3n** were obtained in 70–82% yields (Table 1). The structures of the β,γ-unsaturated ketones thus obtained were unambiguously established on the basis of their spectral data (IR, NMR, MS; given as Electronic supplementary information) and finally by comparing with authentic samples.

3a: ^1H NMR ($CDCl_3$) δ 3.81 (d, $J = 6.5$, 2H, CH_2CO), 5.18 (dd, $J = 9$, ~1.5, 1H, $H_2C{=}C$), 5.20 (dd, $J = 17.6$, 1.5, 1H, $H_2C{=}C$), 5.98 (m, 1H, $CH{=}CH_2$), 7.62 (t, $J = 8$, 2H, aromatics), 7.73 (t, $J = 8$, 1H, aromatic). 8.03 (d, $J = 8$, 2H, aromatics); IR (KBr) 1695 (C=O), 1670 (C=C) cm^{-1}; EI-MS: m/z 146, 145, 105, 77, 51, 41. Anal. calcd for $C_{10}H_{10}O$: C, 82.15; H, 6.90; found: C, 82.09; H, 6.83.

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