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LETTERS

One-pot synthesis of polyfunctionalized α,β-unsaturated nitriles from nitroalkanes

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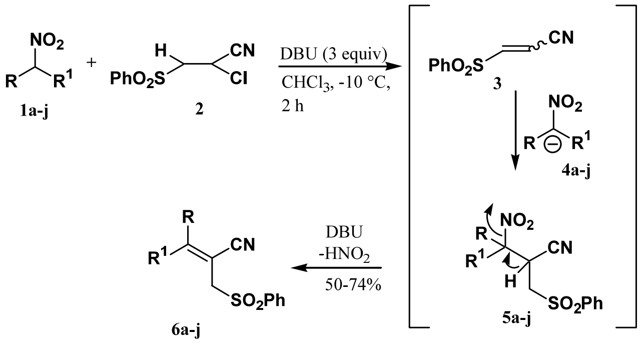
Abstract—The reaction of nitroalkanes with 2-chloro-3-phenylsulfonylpropanenitrile, in the presence of three equivalents of DBU at −10°C, allows the synthesis of polyfunctionalized α,β-unsaturated nitriles. The method proceeds through three different reactions carried out in a tandem sequence, allowing the one-pot formation of the α,β-unsaturated nitriles, generally, with complete *E* stereochemistry.

The synthesis of α,β-unsaturated nitriles is of great interest in synthesis since the nitrile group represents one of the classical functional groups of organic chemistry and conjugated examples are versatile reagents which have been extensively used as electrophilic acceptors and as key precursors in the synthesis of different heterocycles.[1–4] There are several general methods for the preparation of α,β-unsaturated nitriles including: (*i*) the alkenation of either aldehydes or ketones (Wittig or Wittig–Horner condensations) and modification on this theme; (*ii*) displacement of halide ion from vinyl halides by cyanide ion; (*iii*) direct reduction from α,β-alkylenenitriles or via vinyl cuprates; and (*iv*) elimination, such as dehydration of oximes.[3]

In this letter, a new synthetic approach to the one-pot, stereoselective preparation of polyfunctionalized (*E*)-α,β-unsaturated nitriles is presented. Our procedure is based on two recent reports: (*i*) from our laboratory, in which we found that reactions of nitroalkanes with electrophilic alkenes bearing two electron-withdrawing groups in the α- and β-positions, allow the one-pot formation of unsaturated derivatives with enhanced *E* stereoselectivity by a tandem Michael addition-elimination,[5] and (*ii*) by Grayson and Bradley, who reported the in situ production of 3-phenylsulfonylprop-2-enenitrile **3**, under basic conditions.[6] Thus, as reported in Scheme 1, the key idea of our method is the use of nitroalkenes **1** as nucleophiles, DBU as base, and 2-chloro-3-phenylsulfonylpropanenitrile **2** as precursor of the Michael acceptor **3**. Reacting a stoichiometric amount of nitroalkane **1** and nitrile **2**, in $CHCl_3$ in the presence of DBU (3 equivalents), at −10°C, led to the one-pot synthesis of the conjugated nitriles **6**.

The reaction firstly proceeds through the base induced elimination of HCl from **2** to give **3**, with the simultaneous formation of the carbanions **4** that, by a conjugate addition, give Michael adducts **5** which are prone to immediate nitrous acid elimination under our basic reaction conditions, allowing the one-pot formation of functionalized α,β-unsaturated nitriles with complete *E* selectivity (only compounds **6d** and **6i** were obtained as a mixture of *E*/*Z* isomers, in 6:4 and 7:3 ratios, respectively).

It is important to point out that the conjugated nitriles **6** possess the sulfone moiety as an extra function, and it



Scheme 1.

Keywords: nitriles; α,β-unsaturated; nitroalkanes; one-pot synthesis; Michael addition.

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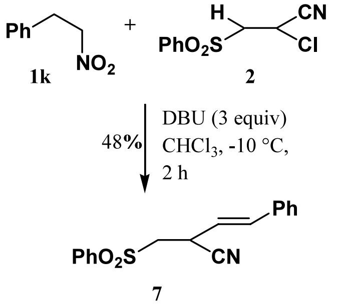
Table 1.

Entry	R	R^1	Yield[a] (%)
a	-$(CH_2)_5$-		63
b	-$(CH_2)_4$-		64
c	CH_3	CH_3	68
d	CH_3CH_2	H	61[b]
e	$CH_3CH_2CH_2$	H	74
f	$CH_3(CH_2)_2CH_2$	H	70
g	$CH_3(CH_2)_3CH_2$	H	71
h	$THPOCH_2$	H	51
i	$CH_3C(OCH_2CH_2O)CH_2$	H	50[c]
j	$CH_3OOCCH_2(CH_2)_3$	H	66

[a] Yields of pure, isolated products.

[b] As *E*/*Z* isomers (6:4).

[c] As *E*/*Z* isomers (7:3).



Scheme 2.

is well known that these kinds of electrophilic nitriles are highly useful substrates in organic synthesis, and are difficult to prepare by other methods.[7] The synthetic results of the reactions presented in Table 1 show that the yields are satisfactory (50–74%), but it must be considered that these are the overall yields of three different steps [(1) HCl elimination from **2** to **3**; (2) conjugate addition of **4** to **3**, and (3) nitrous acid elimination of **5** to **6**]. The method works well with both primary and secondary nitro compounds and with a variety of functionalized nitroalkanes (**1h–j**), so that the final products include several interesting functionalities that could allow further manipulation.

When 2-phenylnitroethane **1k** was used as the starting material, the reaction produced the β,γ-unsaturated nitrile **7** in only 48% yield (Scheme 2), probably due to the favored conjugation with the aromatic structure.

In summary, mono- and polyfunctionalized α,β-unsaturated nitriles are now readily available compounds, accessible from nitroalkanes **1** and 2-chloro-3-phenylsulfonylpropanonitrile **2** by a simple procedure involving three different reactions, carried out in a tandem sequence, under very mild reaction conditions, and using simple and economical chemicals.

Typical procedure: To a stirred solution of nitro-compound **1a** (0.129 g, 1 mmol) in $CHCl_3$ (6 mL) at −10°C, DBU (0.456 mL, 3 mmol) was added. After stirring for 10 min, a solution of 2-chloro-3-phenylsulfonylpropanenitrile **2** (0.229 g, 1 mmol) in $CHCl_3$ (3 mL) was slowly added and the reaction was stirred for a further 2 h at −10°C. Then, the reaction was diluted with $CHCl_3$ (50 mL) and the resulting solution was treated with 0.2N HCl and extracted with $CHCl_3$ (3×30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product **6a** which was purified by flash chromatography over neutral alumina (EtOAc/cyclohexane, 8:2). Yield 0.174 g (63%) of a white solid, mp = 137°C; IR: $\nu = 1639$, 2216 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ (ppm) 1.48–1.78 (m, 6H), 2.17–2.22 (m, 2H), 2.47–2.53 (m, 2H), 3.98 (s, 2H), 7.56–7.96 (m, 5H). ^{13}C NMR (75 MHz, $CHCl_3$) δ (ppm) 25.7, 27.5, 28.1, 31.5, 35.8, 56.1, 94.8, 117.3, 128.9, 129.7, 134.7, 138.1, 170.1. Anal. calcd for $C_{15}H_{17}NO_2S$ (275.36) C, 65.43; H, 6.22; N, 5.09. Found C, 65.55; H, 6.17; N, 5.00.

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