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Uncatalyzed conversion of linear α-nitro ketones into amides by reaction with primary amines under solventless conditions

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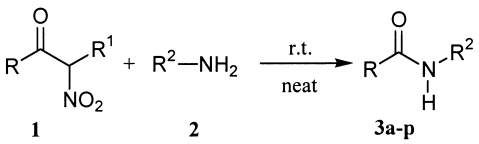
Abstract—The reaction of linear α-nitro ketones with primary amines allows the formation of amides through the cleavage of the carbon–carbon bond between the carbonyl group and the carbon-nitro group moiety, promoted by the nucleophilic effect of the amine. The reaction is performed at room temperature, without any catalyst and/or solvent.

The use of α-nitro ketones in organic synthesis is of great interest.[1–17] In fact, given the well-known chemical differences between the carbonyl and carbon-nitro groups, their juxtaposition on two adjacent positions offers a new reactivity pattern, peculiar to this class of compounds. However, cyclic and linear α-nitro ketones have different reactivities and are utilized differently: (i) 2-nitrocycloalkanones are of great importance because a typical reactivity of these compounds is the cleavage of the C(1)–C(2) bond by the action of external[1,14] or internal[2] nucleophiles under different catalytic conditions (basic, acidic, reductive, oxidative, etc.), (ii) linear 2-nitro ketones being far less prone to carbon–carbon cleavage are mainly employed in the synthesis of ketones,[3] α-deuterated ketones,[3] alkanes,[5] β-nitroalkanols,[15] and many important natural products,[3,4,6] by manipulation of the carbonyl or/and the nitro group.

Previously, we treated α-nitro ketones with primary amino derivatives (NH_2–Y; Y=OH, NHTs) in order to obtain the corresponding imines,[3,5,12,16,17] without observing any carbon–carbon cleavage of the starting α-nitro ketone. Now, we wish to report a surprising result obtained by the reaction of the title nitro ketones with primary aliphatic and aromatic amines. As reported in Scheme 1, treatment of an open chain α-nitro ketone **1** with a primary amine **2** (mole ratio **1/2**=1:5), without any catalyst and solvent, allows, after an appropriate time and at room temperature, the cleavage of the carbon–carbon (carbonyl and carbon atom bearing the nitro group) bond with the formation of the amide **3**.



1 **2** **3a-p**

Scheme 1.

We tried the reaction with different, selected α-nitro ketones and amines in order to verify the synthetic potential of our method. Although this reaction produces, in general, good yields (Table 1) of the compound **3**, the reaction times and the efficiency seem to be dependent upon the bulk of the alkyl groups R^1 (**3i**) and R^2 (**3i**,**m**). Moreover, when the amine is an aromatic one (R^2=Ph, **3dh**,**l**,**p**) the efficacy of the reaction, due to reduced nucleophilicity of the amine, decreases.

Table 1. Synthesis of amides **3** from linear α-nitro ketones **1**

	R	R^1	R^2	Reaction time (h)	Yield[a] (%) of **3**
a	$PhCH_2CH_2$	CH_3CH_2	$(CH_3)_2CH$	15	Quant.
b	$PhCH_2CH_2$	CH_3CH_2	$CH_3(CH_2)_4$	15	Quant.
c	$PhCH_2CH_2$	CH_3CH_2	$PhCH_2$	15	Quant.
d	$PhCH_2CH_2$	CH_3CH_2	Ph	168	75
e	Ph	CH_3	$(CH_3)_2CH$	4	Quant.
f	Ph	CH_3	$CH_3(CH_2)_4$	5	Quant.
g	Ph	CH_3	$PhCH_2$	5	Quant.
h	Ph	CH_3	Ph	312	20
i	$CH_3(CH_2)_3$	$(CH_3)_2CH$	$(CH_3)_2CH$	240	42
j	$CH_3(CH_2)_3$	$(CH_3)_2CH$	$CH_3(CH_2)_4$	15	Quant.
k	$CH_3(CH_2)_3$	$(CH_3)_2CH$	$PhCH_2$	15	Quant.
l	$CH_3(CH_2)_3$	$(CH_3)_2CH$	Ph	960	31
m	Ph	H	$(CH_3)_2CH$	140	10
n	Ph	H	$CH_3(CH_2)_4$	5	Quant.
o	Ph	H	$PhCH_2$	6	Quant.
p	Ph	H	Ph	150	6

[a] Yield of pure isolated product.

Keywords: nitro ketones; amides; carbon–carbon bond; cleavage; solventless.

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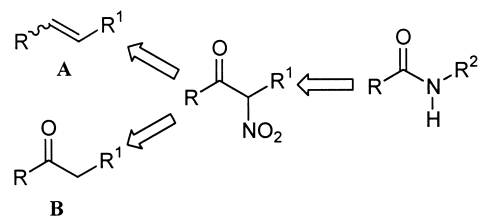

Scheme 2.

Our discovery is the first example of the cleavage of linear α-nitro ketones by an amine and represents a further extension of the potential of the α-nitro ketones in organic synthesis and, moreover, since these compounds can be easily prepared from alkenes[1,14,18] **A** or ketones[1,14,19] **B**, our methodology can be regarded as a formal way to convert alkenes or ketones into amides (Scheme 2).

In conclusion, we report a new reactivity of α-nitro ketones, under environmentally friendly conditions, with potential applications in organic synthesis.

1. Experimental

1.1. General

^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO at 50 and 200 MHz, respectively, on a Varian Gemini instrument; *J* values are given in Hz. IR spectra were recorded with a Perkin–Elmer 257 spetrcophotometer. Mass spectra were determined on a capillary GC/MS operating in the split mode with helium carrier gas and fitted with mass-selective detector (MDS). The reactions were monitored by TLC or GC performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran Glass, stationary phase OV1. Microanalyses were performed using a Fisons model EA 1108. The products were purified by flash chromatography on Merck silica gel.

1.2. General procedure for the conversion of linear α-nitro ketones 1 into amides 3

The amine **2** (50 mmol) is mixed with the α-nitro ketone **1** (10 mmol) and the mixture is left at room temperature for the appropriate time (see Table 1). Then, diethyl ether (100 mL) was added, the organic layer was washed with 2N HCl (in order to remove the excess of the amine, 3×10 mL), dried ($MgSO_4$), evaporated and the crude compound **3** is then purified by flash chromatography (EtOAc/petroleum ether, 3:7).

1.2.1. Compound 3a. Yield=1.906 g (quant.); light yellow solid, mp=89–90°C. Spectroscopic data consistent with the literature.[20]

1.2.2. Compound 3b. Yield=2.183 g (quant.); light yellow waxy solid. IR (film) 3300, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, *J*=7.0 Hz), 1.1–1.3 (m, 4H), 1.3–1.4 (m, 2H), 2.44 (t, 2H, *J*=7.6 Hz), 2.94 (t, 2H, *J*=7.6 Hz), 3.1–3.2 (m, 2H), 5.28 (bs, 1H), 7.1–7.2 (m, 2H), 7.3–7.4 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 139.1, 128.7, 127.8, 127.4, 39.4, 36.5, 31.5, 29.3, 27.4, 24.5, 15.3; EI MS 219 (M^+), 204, 190, 176, 148, 133, 105, 91 (100), 77, 44. Anal. calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.75; H, 9.74; N, 6.31.

1.2.3. Compound 3c. Yield=2.38 g (quant.); light yellow solid, mp=82–83°C. Spectroscopic data consistent with the literature.[21]

1.2.4. Compound 3d. Yield=1.68 g (75%); light yellow solid, mp=97–99°C. Spectroscopic data consistent with the literature.[22]

1.2.5. Compound 3e. Yield=1.62 g (quant.); colourless solid; mp=102–103°C. Spectroscopic data consistent with the literature.[23]

1.2.6. Compound 3f. Yield=1.9 g (quant.); colourless solid; mp=32–34°C. Spectroscopic data consistent with the literature.[24]

1.2.7. Compound 3g. Yield=2.1 g (quant.); colourless solid; mp=128–130°C. Spectroscopic data consistent with the literature.[25]

1.2.8. Compound 3h. Yield=0.394 g (20%); colourless solid; mp=160–162°C. Spectroscopic data consistent with the literature.[26]

1.2.9. Compound 3i. Yield=0.6 g (42%); colourless waxy solid. Spectroscopic data consistent with the literature.[27]

1.2.10. Compound 3j. Yield=1.7 g (quant.); colourless waxy solid. IR (film) 3294, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85–0.98 (m, 6H), 1.24–1.70 (m, 10H), 2.16 (t, 2H, *J*=7.5 Hz), 3.24 (q, 2H, *J*=6.6 Hz), 5.48 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 173.0, 39.5, 36.7, 29.4, 29.1, 27.9, 22.4, 22.4, 14.0, 13.8; EI MS 171 (M^+), 156, 142, 129, 114, 85 (100), 73, 57, 41, 30. Anal. calcd for $C_{10}H_{21}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.98; H, 12.04; N, 9.74.

1.2.11. Compound 3k. Yield=1.9 g (quant.); colourless solid; mp=39–41°C. IR (film) 3291, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J*=7.1 Hz), 1.21–1.47 (m, 2H), 1.56–1.75 (m, 2H), 2.23 (t, 2H, *J*=7.5 Hz), 4.45 (d, 2H, *J*=5.5 Hz), 5.77 (bs, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 173.0, 138.4, 128.7, 127.8, 127.5, 43.6, 36.6, 27.8, 22.4, 13.8; EI MS 191 (M^+), 176, 162, 149, 106, 91 (100), 77. Anal. calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.44; H, 9.02; N, 7.24.

1.2.12. Compound 3l. Yield=0.549 g (31%); colourless solid; mp=61–63°C. IR (film) 3291, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=7.0 Hz), 1.20–1.48 (m, 2H), 1.56–1.75 (m, 2H), 2.36 (t, 2H, *J*=7.0 Hz), 7.03–7.61 (m, 6H), 7.45–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.4, 137.8, 128.8, 124.0, 119.7, 37.4, 27.5, 22.2, 13.6; EI MS 177 (M^+), 148, 135, 120, 93 (100), 77. Anal. calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.65; H, 8.64; N, 7.81.

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