C-Acylation of Nitromethane. A Synthetic Route to α-Nitroketones

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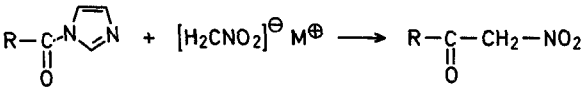
Historically the *C*-acylation of nitromethane to produce α-nitroketones has been carried out with only limited success. In 1903 Gabriel reported a poor yield of the α-nitroketone from the reaction of phthalic anhydride with sodium methanenitronate[1]. Other applications of this general process using either acyl halides, anhydrides, or activated esters have proved the reaction to be of little synthetic value[2]. Despite the ambident nature of the methanenitronate anion, *O*-acylation was found generally favored over *C*-acylation, and the resulting nitronic anhydrides were subject to rearrangement[3]. The apparent lack of *C*-nucleophilicity of the anionic species has been cleverly handled via the umpolung[4] concept that makes use of the doubly metalated complex, $[R-\bar{C}=NO_2]^{2\ominus}2Li^{\oplus}$, that gives good yields of both *C*-acylated and *C*-alkylated nitroparaffins[5].

Herein is reported a simple, direct procedure that allows the preparation of a variety of α-nitroketones **3a–i** via a direct acylation of sodium or potassium methanenitronate **2** with the appropriate *N*-acylimidazole **1a–i**.



1a-i **2** **3a-i**

The acylating agents **1a–i** are easily prepared[6] either *in situ* from the carboxylic acid and 1,1′-carbonyldiimidazole or from the acyl halide and two equivalents of imidazole. The success of the reaction apparently depends upon the unique reactivity of the acylimidazole **1a–i**, similar to that

Table. Preparation of an Physical Constants for α-Nitroketones **3a–i**

Product	R	Base	Yield [%]	m.p.[a] (Lit. m.p.)	Recryst. Solvent	I.R. (KBr)[b] ν [cm^{-1}] C=O, NO_2(as), NO_2(s)	^{1}H-N.M.R. (DMSO-d_6)[c] δ [ppm] α-CH_2	M.S. *m/e* (intensity)[d] $M^{\oplus}$, $M^{\oplus}-CH_2NO_2$
3a	C_6H_5	NaH	32	104–106° (105–106°)[2]	—[e]	1700, 1564, 1334	6.57	165 (33), 105 (100)
3b	2-Cl—C_6H_4	KOC_4H_9-*t*	52	53.5–54.5° (52°)[7]	C_2H_5OH/H_2O	1705, 1563, 1321	6.40	199 (14), 139 (100)
3c	3-Cl—C_6H_4	KOC_4H_9-*t*	72	96–97° (92°)[7]	C_2H_5OH	1710, 1570, 1322	6.53	199 (33), 139 (100)
3d	4-Cl—C_6H_4	NaH	55[f]	164.5–166°	C_2H_5OH	1695, 1565, 1327	6.47	199 (25), 139 (100)
3e	3-O_2N—C_6H_4	NaH	77	93–94° (93°)[7]	C_2H_5OH	1720, 1570, 1332	6.58	210 (13), 150 (100)
3f	3,5-Di-H_3CO—C_6H_3	NaH	88[g]	114–117°	$CHCl_3$/n-C_6H_{14}	1705, 1555, 1325	6.47	225 (91), 165 (24)[h]
3g	3,4-Di-H_3C—C_6H_3	NaH, KOC_4H_9-*t*	83, 85[i]	101–102.5°	$CHCl_3$/n-C_6H_{14}	1700, 1560, 1330	6.42	193 (36), 133 (100)
3h	C_6H_5—CH_2CH_2	NaH	50[j]	69–71°[k]	CH_2Cl_2/ether	1740, 1570, 1317	5.82	193 (2), 133 (3)[l]
3i	CH_3[m]	KOC_4H_9-*t*	56	140.5–142° (139–140°)[9]	C_2H_5OH	—, —, —	5.60	

[a] All m.p. determinations are uncorrected and were carried out using a Thomas-Hoover Unimelt capillary melting point apparatus.

[b] The I.R. spectra were determined on a Digilab FTS-14 pulsed Fourier-transform spectrometer.

[c] The N.M.R. spectra were determined at 90 MHz using either a Bruker WH-90 or a Varian EM-390 instrument; TMS as internal standard.

[d] Mass spectra were determined at 70eV using a Finnigan 1015 quadrupole instrument; all data are normalized with the base peak.

[e] The product was sublimed in vacuo at 80°.

[f] $C_8H_6ClNO_3$ (199.6) calc. C 48.15 H 3.03 Cl 17.76 N 7.02; found 47.95 3.02 18.16 6.91. Compare: *Takamine Kenkyuosko Nempo* **13**, 198 (1961); *C. A.* **57**, 16450 (1962).

[g] $C_{10}H_{11}NO_5$ (225.2) calc. C 53.33 H 4.92 N 6.22; found 53.21 5.15 6.33

[h] Base peak: *m/e* = 151.

[i] $C_{10}H_{11}NO_3$ (193.2) calc. C 62.17 H 5.74 N 7.25; found 62.01 5.80 7.21

[j] $C_{10}H_{11}NO_3$ found C 62.13 H 5.95 N 7.20

[k] The crude product recrystallized poorly and was purified by column chromatography over Silica Gel-60 (E. Merck) using methanol as eluent.

[l] Base peak: *m/e* = 91 ($C_7H_7^{\oplus}$).

[m] The compound was isolated as its 2,4-dinitrophenylhydrazone by reaction of the crude, oily ketone with 2,4-dinitrophenylhydrazine in ethanolic hydrogen chloride.

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observed for acyl cyanides[2], which favor *C*-acylation over *O*-acylation of the ambient anion **2**. Although the scope of the reaction has not been extensively explored, the process appears to be of wide utility in the synthesis of both aliphatic and aromatic α-nitroketones. Noteworthy exceptions are the examples of both 2- and 4-nitrobenzoic acids where highly reactive *N*-acylimidazoles were encountered and no α-nitroketones could be detected among the reaction products. In contrast, 3-nitrobenzoic acid gave a 77% yield of the expected 3-nitroacetophenone (**3e**). Procedurally the reaction is simple and offers advantages over existing procedures for the preparation of α-nitroketones[2], including the oxidation of α-nitroalcohols[7]. Either sodium hydride or potassium *t*-butoxide appear equally effective as bases, although the latter is to be preferred on account of its greater ease of handling.

C-Acylation of Nitromethane; General Procedure:

Step A: *Preparation of the acylimidazoles* **1a–i:** A suspension of the appropriate carboxylic acid (10 mmol) and 1,1′-carbonyldiimidazole (12 mmol) in dry tetrahydrofuran (50 ml; distilled from calcium hydride) is heated under reflux for 1 h, by the end of which time a solution has formed. This crude imidazolide preparation is used directly in the condensation step B. Alternatively, where convenient, the imidazolides are prepared and isolated as crystalline solids from the reaction of the acyl halide with two equivalents of imidazole[6].

Step B: *Synthesis of the α-nitroketones:* To a solution of either potassium *t*-butoxide or sodium hydride (12 mmol; see Table) in dry tetrahydrofuran (20 ml) is added nitromethane (25 ml, 2.84 g, 47 mmol) (dried over 4-A sieves). The appropriate imidazolide **1a–i** from the foregoing is added dropwise, with stirring over 10 min. The resultant suspension is heated under reflux for ~16 h and cooled to room temperature. The suspension is filtered, and the crude enolate salt is washed with dichloromethane (2 × 50 ml). Water (~100 ml) is poured *onto*[8] the salt, and the dissolved salt is adjusted to pH 3 with concentrated hydrochloric acid. The suspension is repeatedly extracted with portions of ethyl acetate while maintaining a pH of ~3 by addition of acid. The combined, organic extracts are dried (magnesium sulfate) and evaporated in vacuo to give crude **3a–i**, that are typically purified by recrystallization (see Table).

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