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The Nitration of Activated Carbonyl Compounds in a Two-phase System†

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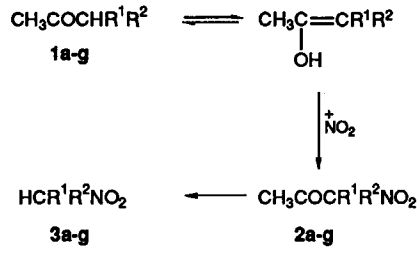
The nitration of activated carbonyl compounds in a two-phase system gives novel possibilities for the synthesis of functional nitro derivatives.

α-Functional nitro compounds (nitroacetic esters, nitroketones, nitroacetonitrile, *etc.*) have wide utility for the synthesis of amino acids, nitroenamines and heterocycles. However, the synthesis of such nitro compounds from salts of nitroalkanes is very dangerous. The nitration of ketones leads to the formation of nitroketones which yield furoxanes and hydroxamic acids;[3] for example, the synthesis of ethyl nitroacetoacetate from ethyl acetoacetate in the mixture acetic anhydride–nitric acid.[4] The instability of the acetic anhydride–nitric acid mixture makes the preparation of functional nitro compounds very difficult.

We have developed an effective nitration method for easily enolizable carbonyl derivatives **1** in a two-phase system: a chloroform (dichloroethane or dichloromethane)–sulfuric acid/nitrate mixture. In this case nitro compounds were easily separated from the organic layer. The deacylation of difunctional nitro derivatives **2**, without their isolation, yielded monofunctional nitro compounds. **3**.‡

Sulfuric acid/nitrate mixtures can be prepared using both nitric acid and ammonium nitrate. A ratio of sulfuric and nitric acids to substrate of 4:1:1 was found to be most promising. When we used potassium or sodium nitrates yields were low



Scheme 1

because of the low solubility of the nitrates in sulfuric acid, and a greater quantity of sulfuric acid present is a reason for the by product discussed earlier.

The experimental data observed in the two-phase system are evidence for electrophilic nitration by the nitronium ion[1] preceding nitration of the active aromatic system under interphase conditions.[7]

The coefficient describing the distribution of substrates between 93% sulfuric acid and chloroform, defined by UV-spectroscopy, was 39.1 for **1a** and 0.02 for **2a**, *i.e.* 97.5% ethyl acetoacetate was extracted into sulfuric acid but after nitration 98% nitroacetoacetic ester was returned into chloroform.

The nitration of ethyl acetoacetate ceased when the concentration of sulfuric acid fell below 85%, *i.e.* when nitronium ions were absent.[8–10] The optimum concentration of H_2SO_4 was 92–93%, confirmed by ^{14}N NMR[8] and UV spectroscopy[9] and thermochemical measurements.[10]

The addition of $NaNO_2$ did not catalyse the reaction, *i.e.* nitric oxides do not take part in this process.[7,11] This also confirms the electrophilic nature of the nitration.

The optimum ratio between the ingredients of the nitric acid mixture and substrate was used in the nitration of the acetoacetate series and other active ketones (Table 1).

When the temperature was increased ethyl nitroacetoacetate was nitrated to ethyl dinitroacetoacetate **2c**. However, **2c** was very easily hydrolysed to ethyl dinitroacetate **3c** which was the major product (90–95%); only 5% of **2c** was isolated in this reaction. The preliminary kinetic data, which were observed by UV spectroscopy at 20°C, confirmed that the first stage of the nitration was faster than the second by two orders of magnitude.

The marked difference between the nitration stages allowed

† Full details will be given later (ref. 1).

‡ *Preparation of the sulfuric acid/nitrate mixtures (for 0.1 mol carbonyl derivative).*

(a) 93% H_2SO_4 (d 1.83, 15.9 cm^3) was added dropwise to 100% HNO_3 (d = 1.5, 4.53 cm^3) with vigorous stirring, T < 15°C.

(b) 93% H_2SO_4 (25 cm^3) was added to NH_4NO_3 (8.4 g) and the mixture was stirred until the salt had dissolved.

General method for the nitration.

The sulfuric acid/nitrate mixture was dropped onto a cooled mixture (−10 to −5°C) of carbonyl derivative (0.1 mol) and $CHCl_3$ (75 cm^3) with vigorous stirring (for length and temperature of the nitration, see Table 1). The organic layer was separated and dried ($NaSO_4$), then solvent was removed under reduced pressure to yield **2a**, **b**, **d–g** or a mixture of **2c** and **3c**.

Synthesis of the salts **2a**, **b**, **f**, **g**.

Solutions of nitroalkanes **2a**, **b**, **f**, **g** in chloroform after nitration were added to an equal amount of potassium acetate in methanol. The solid was filtered and dried in a vacuum desiccator.

General method of deacylation.

Nitroketones **2a–g** were dissolved in twice the volume of methanol containing 10% H_2SO_4. The mixture was kept for 1 h then neutralized by an equal amount of $NaHCO_3$. Methanol was removed under reduced pressure and the residue was mixed with water and extracted with chloroform or ethyl ether. The mixture was dried (Na_2SO_4), solvent was removed, and 3 g solid was recrystallized.

Table 1 Conditions for the nitration (Scheme 1)

Compound	R^1	R^2	Yield for **2a–g** (%)	T (°C)/ reaction time (min)	B.p. (°C)/ mm Hg for **2a–g**	Yield of **3a–g** (%)	B.p. (°C)/ mm Hg for **3a–g**
a	CO_2Et	H	85–97	0/60	62–67/0.3	80–97	105–7/25
b	CO_2Me	H	87–98	0/50	60–65/0.5	80–97	99–100/25
c	CO_2Et	NO_2	[a]	20/180	78–80/2	97[b]	68–70/2
d	CO_2Et	CH_3	55–60	10/60	95/1	80–95	100–5/10
e	CO_2Et	CF_3	50–53	20/180	75–78/8	90–95	75/25
f	CN	H	65–75	−2/60	91–93[c] hexane	70–85	55/2
g	CH_3CO	H	30	10–15/20	52–55/5 (ref. 5)	50	45.6[c] (ref. 6)

[a] Obtained from **3c**, yield of **2c** low (5%). [b] Yield from **1a**. [c] M.p. (°C).

us to develop selective methods for the one-step synthesis of nitro- and dinitro-acetates[12] from ethyl acetoacetate. Comparing the synthesis of **2c** from the monomalonic ester[13] our method is simpler and has more accessible starting materials with higher yields.

The nitration of ethyl 2-methylacetoacetate allows us to obtain promising α-methyl amino acid and peptide precursors **3d**.[14] The consecutive insertion of CF_3 and NO_2 groups into **1a** is a very useful method for the synthesis of the CF_3-nitroacetic ester, which would be an interesting material for the construction of α-CF_3-amino acids.[15] Alkyl nitroacetic esters **2d** and **2e** are interesting as precursors for α-methyl and α-CF_3-threonine.

Preliminary UV-spectroscopic data showed that the time corresponding to the nitration of 50% **1a** and **1d** to **2a** and **2d** under optimum conditions (0°C, equimolar amount of HNO_3) were 12 and 14 min, respectively, whereas analogous nitration of **1e** took place only on increasing the temperature to 20°C during 50 min.

Ethyl acetoacetate **1a** was nitrated more easily than ethyl α-methylacetoacetate **1d** but α-CF_3-acetoacetate **1d** was nitrated more slowly than **1d** and only by increasing the temperature. This fact evidently results from both a difference in the enolization abilities of **1a**, **1d** and **1e**, and by the different activity of the enols themselves.

The fact that mixtures based on acetic anhydride can not be used for nitration derivatives of the ethyl acetoacetates **1c–e** should be noted.

All nitro derivatives were easily deacylated (Table 1) in ethanol or methanol with a catalytic amount of strong acid (H_2SO_4, $HClO_4$, BF_3, *etc.*).

The structures of the compounds obtained were evidenced by both the transformation to well known products **3a–d** and data from NMR (^1H, ^{13}C and ^{14}N), IR and UV spectroscopy.[1]

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