Organic Chemistry

Synthesis of α-functional nitro compounds by the nitration of activated carbonyl compounds in a two-phase system

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2-Nitro-1,3-dicarbonyl and α-nitromonocarbonyl compounds were synthesized in the yields varying from moderate (30 %) to nearly quantitative by the nitration of β-dicarbonyl compounds in a two-phase system: sulfuric/nitric acid mixture—chloroform at −10÷10 °C. The use of phase transfer conditions made it possible to avoid the formation of furoxans as by-products and to simplify the isolation of products. This method is quite common for preparing various α-functional nitro compounds including those containing a CF_3-group.

Key words: nitration, α-functional nitro compounds.

α-Functional nitro compounds (α-FNC), *i.e.*, nitroacetic esters, nitroacetonitrile, nitroketones, *etc.*, are extensively used for the synthesis of amino acids, nitroenamines, and heterocycles.[1–4] However, the methods for preparing α-FNC, unlike those for preparing β-FNC, γ-FNC, and so on, are not particularly advanced, since the methods for the functionalization of nitroalkanes are limited by the hazards in dealing with their salts; on the other hand, nitration of ketones is accompanied by the conversion of the resulting nitroketones to furoxans[5] and hydroxamic acids.[6]

In the present work we described an approach to the preparation of α-FNC by means of electrophilic nitration of the enolized carbonyl compounds **1** followed by deacylation of the resulting difunctional nitro derivatives **2** to form the target monofunctional nitro compounds **3** (Scheme 1, Table 1).

The nitration of ethyl acetoacetate (AA) in the acetic anhydride—nitric acid homogeneous system to give ethyl nitroacetoacetate (NAA, **2a**) in a high yield (up to 97 %, according to GLC) has been described previously.[9] The results of this work can be satisfactorily reproduced, however, producing compounds **2a** and **3a** in large quantities is complicated by the fact that the temperature of the process needs to be thoroughly moni-

Scheme 1

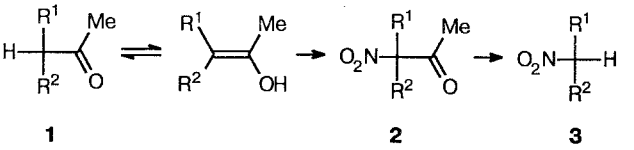

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Table 1. Conditions for the preparation of nitro carbonyl compounds according to Scheme 1

1	R^1	R^2	T/°C (reaction time)	2		3	
				Yield (%)	B.p./°C (*p*/Torr)	Yield (%)	B.p./°C (*p*/Torr)
a	COOEt	H	0 (1 h)	85—97	62—67(0.3)	80—97	105—107(25)
b	COOMe	H	0 (50 min)	87—98	60—65(0.5)	80—97	99—100(25)
c	COOEt	NO_2	20 (3 h)	—[a]	78—80(2)	97[b]	68—70(2)
d	COOEt	CH_3	10 (1 h)	55—60	95(1)	80—95	100—105(10)
e	COOEt	CF_3	20 (3 h)	50—53	75—78(8)	90—95	75(25)
f	CN	H	−2 (1 h)	65—75	91—93[c] (from hexene)	70—85	55(2)
g	CH_3CO	H	10—15 (20 min)	30	52—55(5)[c,d]	50	45.6[c,d]

[a] Forms as a mixture with **3c**, the yield of **2c** does not exceed 5 %. [b] The yield over two steps based on the starting ester **2a**. [c] M.p./°C. [d] The literature data.[7,8]

tored, in order to prevent **2a** from readily converting to bis(ethoxycarbonyl)furoxan which would decrease the yield of **2a** and can sometimes cause the ejection of the reaction mixture from the reaction vessel. Unsuccessful attempts to use mixtures of Ac_2O and HNO_3 to prepare other nitro derivatives have been undertaken: NAA and α-CF_3-AA did not undergo nitration, acetylacetone was oxidized, and the reaction of α-Me-AA afforded 1,1-dinitroethane in an 8 % yield, rather than the expected products **2d** and **3d**.

We have developed an efficient method for the nitration of carbonyl compounds in the two-phase system: sulfuric/nitric acid mixture—chloroform (or dichloroethane, or methylene chloride). The product of nitration in this method remains in the organic layer and can be readily isolated after the separation of the chloroform solution and evaporation of the solvent. For example, ethyl acetoacetate **1a** is nitrated to give nitro derivative **2a** in a quantitative yield. Sulfuric-nitric acid mixtures can be based on either nitric acid or ammonium nitrate; in the latter case the yields of the product are lower by 10—15 %, but are considerably more reproducible. When sodium or potassium nitrate is used instead of NH_4NO_3, the yields of **2a** decrease, because these nitrates are poorly soluble in H_2SO_4; the use of a great excess of the latter results in the conversion of **2a** to bis(ethoxycarbonyl)furoxan.

For the phase-transfer nitration of activated aromatic compounds with dilute solutions of HNO_3 the radical-cation mechanism has been previously proposed.[10] We suggest that the phase-transfer nitration of compounds **1a—g** occurs as electrophilic nitration by the nitronium cation, after the carbonyl compound has been extracted to the sulfuric-nitric layer, and the subsequent reextraction of the resulting nitrocarbonyl compound **2** to chloroform:

$$\mathbf{1a}\ (CHCl_3) \rightleftharpoons \mathbf{1a}\ (H_2SO_4)$$
$$\mathbf{1a}\ (H_2SO_4) \longrightarrow \mathbf{2a}\ (H_2SO_4)$$
$$\mathbf{2a}\ (H_2SO_4) \rightleftharpoons \mathbf{2a}\ (CHCl_3)$$

The following experimental data attest to this mechanism:

1. Acetoacetic ester is not nitrated when the concentration of H_2SO_4 in the mixture is lower than 85 %, and the optimal concentration of H_2SO_4 is 92—93 %; this is in agreement with the data[11] from ^{14}N NMR, Raman, and UV spectra[12] and thermochemistry[13] on the content of nitronium ions in sulfuric-nitric acid mixtures: at concentrations of H_2SO_4 lower than 85 % nitronium ions are practically missing, whereas at H_2SO_4 concentrations higher than 93 %, nitric acid is entirely converted to nitronium ions.

2. The reaction is not catalyzed by the addition of $NaNO_2$, *i.e.*, nitrogen oxides do not participate in the process.[10,14]

3. The coefficients of the distribution of substrates between 93 % H_2SO_4 and $CHCl_3$, which we have determined by spectrophotometry, amount to 39.1 for **1a** and 0.02 for **2a**, *i.e.*, 97.5 % of the ethyl acetoacetate is extracted to H_2SO_4, and 98 % of the ethyl nitroacetoacetate returns to $CHCl_3$ after nitration. Naturally, under the actual conditions of nitration **2a** is almost entirely extracted to $CHCl_3$, since the volume of H_2SO_4 is substantially smaller (see Experimental).

The nitration of a number of acetoacetic esters and other activated ketones was carried out under the optimal conditions chosen, including the optimal ratio between the components of the nitrating mixture and the carbonyl compound (Table 1). Methyl acetoacetate is also nitrated in high yields, however, *tert*-butyl acetoacetate decomposes under these conditions to give no identified products, which is in agreement with the well known instability of the *tert*-butyl protection in acid media.

Ethyl nitroacetoacetate is further nitrated nearly quantitatively in the same mixture at a higher temperature to give ethyl 2,2-dinitroacetoacetate **2c** which, however, can be isolated in only small amounts (5 %) owing to its tendency to hydrolysis, and the major reaction product is ethyl dinitroacetate (**3c**, 90—95 %). According to the preliminary kinetic data, which we obtained by UV

Table 2. The ^1H, ^{14}N, and ^{19}F NMR chemical shifts (ppm) and $^1H-^1H$ and $^1H-^{19}F$ spin—spin coupling constants (*J*/Hz)

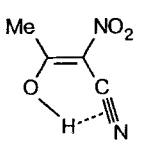
Compound	NMR ^1H					NMR ^{14}N	NMR ^{19}F
	$CH_3(C_2H_5)$	CH_3CO	$CH_2(C_2H_5)$	CH	Other		
2a	1.31 t (7.1)	2.45 s	4.36 q (7.1)	6.63 s	—	−12.90	—
2c	2.24 t (5.0)	2.51 s	4.53 q (5.0)	—	—	−28.20	—
2d	1.30 t (7.2)	2.35 s	4.32 q (7.2)	—	1.94 s (CH_3)	−8.70	—
2e	1.3 t (7.2)	2.50 s	4.48 q (7.2)	—	—	−22.90	−65.53 s
2f	—	2.50 s	—	—	13.85 br.s (OH)	−16.60 −104.80 (CN)	—
2g	—	2.41 s	—	—	11.38 br.s (OH)	−12.20	—
3c	2.26 t (4.4)	—	4.18 q (4.4)	5.60 s	—	−27.90	—
3e	1.33 t (7.1)	—	4.39 q (7.1)	5.71 q $^2J_{H-F}$ = 11.0	—	−23.20	−68.54 d ^2J = 11.0

spectroscopy at 20 °C, the rate of the introduction of the first nitro group is higher than that of the second nitro group by 1—2 orders of magnitude.

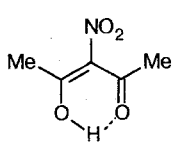
The considerable distinction between the rates of nitration made it possible to develop selective one-step preparative-scale procedures for the synthesis of nitro- and dinitroacetoacetic esters[15] directly from acetoacetic ester. The method for the synthesis of dinitroacetoacetic ester proposed by us offers the advantages of simplicity, yield, and the availability of the starting compounds as compared with synthesis from malonic acid monoester.[16]

Nitration of ethyl 2-methylacetoacetate allowed us to reach ethyl 2-nitropropionate, which is a promising precursor of α-methylamino acids and peptides based on them. The successive introduction of CF_3 and NO_2 groups into AA is a convenient approach to ethyl CF_3-nitroacetate, which may present considerable interest for developing novel ways of assembling the skeleton of α-CF_3-amino acids.[18] Ethyl nitroacetoacetates **2d** and **2e** may be of interest as precursors of α-methyl and α-CF_3-threonine. Cyanoacetone gives nitrocyanoacetone **2f** in a high yield; acetylacetone affords nitroacetylacetone **2g**. Nitroacetone decomposes giving no products that can be identified.

It should be noted that compounds **2f** and **2g**, in contrast to **2a**,[19] are wholly enolized. The ^1H NMR spectrum of **2f** exhibits signals at 2.5 ppm (CH_3) and 13.85 ppm (OH), while signals associated with the CH-group are missing from the ^{13}C NMR spectrum. The IR spectrum does not exhibit the band at 1740 cm^{-1} corresponding to the keto group and exhibits a band at 1480 cm^{-1} associated with the bending vibrations of the OH group. These data allow the enol structure to be assigned to compound **2f**. However, the band at 3450 cm^{-1} which is also associated with the OH group is absent from the spectrum. In analogy with the reported data,[20] we assume that compound **2f** has the *E* structure with an intramolecular hydrogen bond.



(*E*)-2f



2g

Based on the facts that the ^1H NMR spectrum of compound **2g** exhibits only one signal corresponding to two CH_3 groups, while the ^{13}C NMR spectrum exhibits a signal from two CH_3 groups and one signal from two CO groups we believe that compound **2g** exists as a six-membered chelated ring.

Deacylation of NAA as well as compounds **2c—g** readily occurs through the action of EtOH or MeOH in the presence of catalytic amounts of strong acids: H_2SO_4, $HClO_4$, or BF_3 (Table 1).

The structure of the resulting compounds has been confirmed both by their conversion to the known compounds **3a—d,f,g** and on the basis of the combination of data from ^1H, ^{13}C, ^{14}N, ^{19}F-NMR, IR, and UV spectra (Tables 2, 3, and 4).

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250.13 MHz and 235.34 MHz, respectively. The ^{13}C and ^{14}N NMR spectra were obtained on a Bruker AM-300 spectrometer operating at 75.47 MHz and 21.69 MHz with internal standards: Me_4Si for ^1H and ^{13}C NMR spectra, $FCCl_3$ for ^{19}F NMR spectra, and nitromethane for ^{14}N NMR spectra. IR spectra were recorded on a UR-20 spectrophotometer and UV spectra were run on a Specord UV-VIS instrument.

Ethyl 2-methylacetoacetate,[21] cyanoacetone,[22] and ethyl α-trifluoromethylacetoacetate[23] were prepared by known procedures. All of the carbonyl compounds were freshly distilled.

The general procedure for nitration

1. Preparation of sulfuric-nitric acid mixtures (for 0.1 mol of a carbonyl compound).

A. 15.9 mL of 93 % H_2SO_4 (d = 1.83) was added to 4.53 mL of 100 % HNO_3 which was vigorously stirred and cooled below 15 °C.

Table 3. The ^{13}C NMR chemical shifts and $^{13}C—^{1}H$ and $^{13}C—^{19}F$ spin—spin coupling constants

Compound	δ (J/Hz)						
	$CH_3(C_2H_5)$	CH_3CO	$CH_2(C_2H_5)$	$C—NO_2$	COO	C=O	Other
2a	13.66 q.t (127.5; 2.8)	27.71 q (130.0)	64.00 t.q (150.0; 4.5)	93.72 d.q (151.2; 3.2)	159.98 t.d (3.5; 7)	190.78 q (6.6; 4.5)	—
2c	13.60 q.t (128.0; 3.0)	26.93 q (133.0)	66.61 t.q (145.0; 4.5)	*	155.48 t (3.5)	185.21 q (7.1)	—
2d	13.66 q.t (127.7; 3.2)	25.99 q (129.4)	63.74 t.q (148.8; 4.8)	98.36 q.q (7.2; 3.2)	163.80 t.q (3.2; 3.0)	194.27 q.q (7.0; 3.1)	19.35 q (133.0) CH_3
2e	13.59 q.t (130.0; 2.8)	27.06 q (134.0)	65.41 t.q (146.0; 5.0)	99.15 q $^2J_{C-F}$ = 28.0	157.61 t (3.5)	186.44 q (6.8)	119.20 q (285.0) CF_3
2f	—	21.18 q (130.0)	—	109.93 q (4.3)	—	182.66 q (6.1)	109.86 s (CN)
2g	—	24.19 q (130.8)	—	134.92 s (2.0)	—	191.63 q (6.1)	—
3c	13.47 q.t (130.9; 2.8)	—	66.11 t.q (151.0; 4.4)	106.26 d (166.0)	155.31 d.t (4.8; 3.3)	—	—
3e	13.76 q.t (126.9; 2.8)	—	64.95 t.q (149.8; 4.3)	85.45 d.q (152.6; 34.6)	157.45 t.d (3.2; 6.7)	—	119.13 q.q (281.6; 14.3) CF_3

* Is not exhibited.

B. 25 mL of 93 % H_2SO_4 was added to 8.4 g of NH_4NO_3, and the mixture was stirred until the salt entirely dissolved.

2. The conduction of the nitration. At −10÷−5 °C the sulfuric/nitric acid mixture was added to a vigorously stirred solution of carbonyl compound **1** in 75 mL of $CHCl_3$. After the addition, the mixture was stirred (the temperature and duration of the process are given in Table 1) and the chloroform layer was separated and dried with Na_2SO_4. The solvent was evaporated, and the residue was used either for the isolation of pure compounds **2a—g** and their salts or for deacylation to give compounds **3a—g**.

Nitrocyanoacetone **2f**. Found (%): C, 37.50; H, 3.15; N, 21.85. $C_4H_4N_2O_3$. Calculated (%): C, 37.62; H, 3.65; N, 21.63.

Table 4. IR and UV spectra of nitrocarbonyl compounds

Compound	IR spectrum/cm^{-1}	UV spectrum* λ/nm
2a	—	326 (ε = 13880)
2f	2240 (CN); 1600 (C=C); 1570$\nu_{as}(NO_2)$; 1425$_{def}$(OH); 1300$\nu_s NO_2$)	328 (ε = 15700)
2d	1760 (CO); 1570$\nu_{as}(NO_2)$; 1440; 1380; 1250$\nu_s(NO_2)$	—
2e	1760 (CO); 1580$\nu_{as}(NO_2)$	—
3e	1770 (CO); 1580$\nu_{as}(NO_2)$	—

* The data for water-soluble salts, see Experimental.

The general procedure for preparing salts 2a, 2b, 2f, and 2g

An equimolar amount of potassium (or sodium) acetate as a saturated methanolic (or ethanolic) solution was added to a chloroform solution of compound **2a**, **2b**, **2f**, or **2g** obtained after nitration. The precipitate was filtered off and dried in a vacuum desiccator. Yield 25—42 %.

The general procedure for deacylation

Intermediates **2a—g** were dissolved in a twofold volume of MeOH or EtOH containing 10 % H_2SO_4. The mixture was held for 1 h and neutralized with a calculated amount of $NaHCO_3$. The alcohol was evaporated on a rotary evaporator, and the residue was poured in water, and extracted with $CHCl_3$ or Et_2O. The organic solvent was evaporated, and the residue was distilled or recrystallized (**3g**).

Ethyl 3,3,3-trifluoro-2-nitropropionate (3e). Found (%): C, 29.86; H, 3.01; F, 28.34. $C_5H_6F_3N_3O_4$. Calculated (%): C, 29.91, H, 3.26, F, 28.07.

References

1. M. T. Shipchandler, *Synthesis*, 1979, 666.
2. (a) D. I. Weisblat and D. A. Lyttle, *J. Am. Chem. Soc.*, 1949, **71**, 3079; (b) T. Shimizu, Y. Hayashi, and K. Teramura, *Bull. Chem. Soc. Japan*, 1985, **58**, 2519.
3. S. G. Zlotin, G. N. Varnaeva, and O. A. Luk'yanov, *Usp. Khim.*, 1989, **58**, 796 [*Russ. Chem. Revs.*, 1989, **58** (Engl. Transl.)].
4. R. H. Fischer and H. M. Weitz, *Synthesis*, 1980, 261.
5. L. I. Khmel'nitskii, S. S. Novikov, and T. I. Godovikova, *Khimiya furoksanov. Stroenie i sintez* [*Chemistry of Furoxans. Structure and Synthesis*], Nauka, Moscow, 1981 (in Russian).
6. T. Simmons and K. Kreus, *J. Org. Chem.*, 1968, **33**, 836.

7. K. K. Babievskii, E. I. Matrosov, and P. V. Petrovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, 2614 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1971, **20**, 2490 (Engl. Transl.)].
8. I. D. Lebedeva, I. L. Ryadnenko, and I. K. Kucherova, *Zh. Fiz. Khim.*, 1968, **42**, 1827 [*Russ. J. Phys. Chem.*, 1968, **42** (Engl. Transl.)].
9. S. Sifniades, *J. Org. Chem.*, 1975, **40**, 3562.
10. M. J. Thompson and P. J. Zeegers, *Tetrahedron Lett.*, 1988, **29**, 2471.
11. D. S. Ross, K. F. Kuhlmann, and R. Malhotra, *J. Am. Chem. Soc.*, 1983, **105**, 4299.
12. M. Sampoli, A. De Santis, and N. C. Marziano, *J. Phys. Chem.*, 1985, **89**, 2864.
13. I. M. Medvetskaya, M. I. Vinnik, T. S. Kopytova, Yu. N. Matyushin, Yu. A. Lebedev, and V. F. Zhilin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 306 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 251 (Engl. Transl.)].
14. A. S. Morkovnik, *Usp. Khim.*, 1988, **57**, 254 [*Russ. Chem. Revs.*, 1988, **57** (Engl. Transl.)].
15. A. L. Laikhter, T. I. Cherkasova, L. G. Mel'nikova, B. I. Ugrak, A. A. Fainzil'berg, and V. V. Semenov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1849 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 1637 (Engl. Transl.)].
16. V. Grakauskas and A. M. Guest, *J. Org. Chem.*, 1978, **43**, 3485.
17. J. Lalonde, D. Bergbreiten, and C. H. Wong, *J. Org. Chem.*, 1988, **53**, 2322.
18. V. P. Kukhar', Yu. L. Yagupol'skii, and V. A. Soloshonok, *Usp. Khim.*, 1990, **59**, 149 [*Russ. Chem. Revs.*, 1990, **59** (Engl. Transl.)].
19. K. K. Babievskii, V. I. Bakhmutov, and V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 1293 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1978, **27**, 1125 (Engl. Transl.)].
20. E. I. Matrosov and K. K. Babievskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1972, 2627 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1972, **21**, 2567 (Engl. Transl.)].
21. A. Brändström and U. Junggren, *Acta Chem. Scand.*, 1969, **23**, 2204.
22. K. Ziegler, H. Erberle, and H. Ohlinger, *Lieb. Ann. Chem.*, 1933, **504**, 94.
23. K. Uneyama and K. Ueda, *Chem. Lett.*, 1988, **5**, 853.

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