Trifluoromethanesulfonyl Azide: A Powerful Reagent for the Preparation of α-Nitro-α-diazocarbonyl Derivatives

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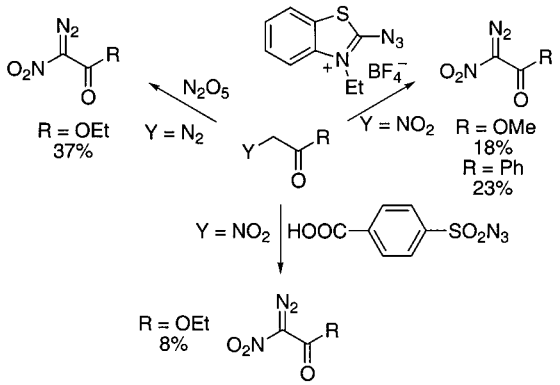
The importance of α-diazocarbonyl reagents has been recognized for a number of years.[1] These reagents are ideal precursors for several transition metal-catalyzed processes including cyclopropanations and X−H insertion reactions (X = C, O, N, S, P, etc.)[2] and the phosphorus or sulfur ylide formation.[3] As part of our research program aiming at developing new methods for the stereoselective synthesis of unnatural amino acids,[4] we became interested in using α-nitro-α-diazocarbonyl derivatives as potential synthetic precursors. Herein, we report a much improved procedure to prepare these reagents which is amenable to the synthesis of a large number of structurally diverse derivatives.

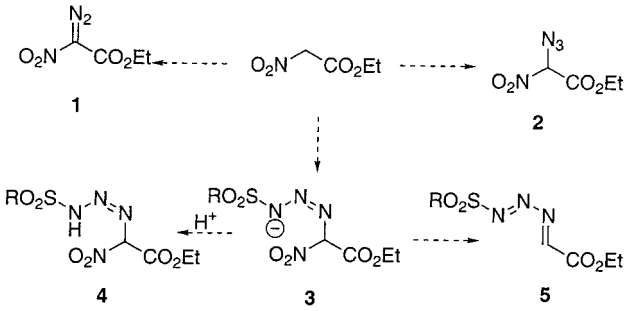
The synthesis of α-nitro-α-diazocarbonyl derivatives has been known for many years, and it involves the treatment of α-nitroesters with 2-azido-3-ethylbenzothiazolium fluoroborate[5] or with *p*-carboxybenzenesulfonazide.[6] Alternatively, they can be prepared by treating diazoester derivatives with dinitrogen pentoxide[7] (Scheme 1).

The first two methods are not very efficient (<20% yield of the diazo compound is obtained) while the latter involves a nonreadily available and unstable reagent (N_2O_5). Although the synthesis of 2-diazo-1,3-dicarbonyl[8] and 2-diazo-3-ketoesters[9] are well-established processes,

Scheme 1



Scheme 2



it has been reported that the popular diazo transfer reagents such as tosyl azide or mesyl azide fail to generate reasonable yields of the desired α-nitro-α-diazocarbonyl derivatives. Among the possible side reactions that can be observed in addition to the formation of the α-azido derivative **2** is the formation of a triazenes **4** and **5** (Scheme 2).[10,11] We reasoned that the use of a stronger electron-withdrawing group (R) on the sulfonyl azide reagent and appropriate base (or conjugate acid) may prevent these undesirable side-reactions and provide an efficient access to this class of synthetically useful compounds.

Several diazo transfer reagents and bases were tested and, gratifyingly, it was found that a hexane solution of trifluoromethanesulfonyl (triflyl) azide reacts smoothly with ethyl nitroacetate in acetonitrile upon addition of pyridine to generate ethyl α-nitro-α-diazoacetate in 88% yield. As a follow-up of this observation, several α-nitroester precursors were prepared,[12] and they all could be converted cleanly to the desired diazo substrate (Table 1).[13] The reactions were typically stirred for 15 h, but in most cases the diazo transfer process occurred rapidly. Bulky esters could also be easily converted into the α-diazo derivatives. For example, *tert*-butyl (entry 4), menthyl (entry 8), and 2-phenylcyclohexyl (entry 9) esters

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(11) For a very good discussion of the various reaction pathways involved in the reactions of stabilized carbanions with arylsulfonyl azide reagents, see: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.

(12) The starting α-nitroesters were prepared according to: Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 875−878.

(13) The characterization data of the known nitrodiazo derivatives were consistent to those reported in the literature: entry 1: Schöllkopf, U.; Tonne, P.; Schäfer, H.; Markusch, P. *Ann. Chem.* **1969**, *722*, 45−51 and ref 7c; entries 4 and 10: see ref 7c.

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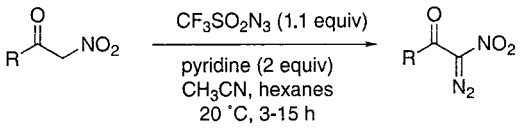
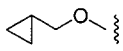
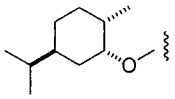
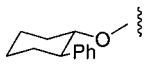
Table 1. Synthesis of α-nitro-α-diazocarbonyl Derivatives



Entry	R-	Yield (%)[a]
1	EtO-	88
2	CH_2=$CHCH_2O$-	88
3	*i*-PrO-	90
4	*t*-BuO-	90
5	*(E)*-PhCH=$CHCH_2O$-	83
6		72
7	4-($PhCH_2O$)$C_6H_4CH_2O$-	90
8		88
9		61
10	Ph-	66
11	*t*-Bu-	65
12	*c*-C_6H_{11}-	67

[a] Isolated yields after column chromatography.

were all converted into the desired compounds under the reaction conditions. In addition, the diazo transfer reaction also occurred cleanly with α-nitroketones,[14] but the yields were generally slightly lower than those observed with the esters (Table 1, entries 10−12).

In conclusion, we have described a highly efficient method for the preparation of α-nitro-α-diazocarbonyl derivatives from the corresponding α-nitrocarbonyl using triflyl azide/pyridine. The use of these compounds in transition metal-catalyzed processes is currently underway and will be reported in due course.

Experimental Section

Although we have not experienced any problem in the handling of these compounds (triflyl azide and the α-nitro-α-diazocarbonyl derivatives), extreme care should be taken when manipulating them due to their explosive nature.[15,16]

Preparation of Triflyl Azide Solution.[17] A solution of sodium azide (3.32 g, 51.1 mmol) and tetrabutylammonium hydrogen sulfate (0.160 g, 0.471 mmol) in distilled water (23 mL) was cooled to 0 °C. A solution of triflic anhydride (6.71 g, 2.0 mL, 23.8 mmol) in hexane (22 mL) was then slowly added, and the resulting clear solution was stirred for an additional 1 h at 0 °C. The reaction mixture was then extracted with hexane (20 mL), and the organic layer was dried over sodium hydroxide pellets and decanted. The hexane solution of triflyl azide was used immediately in the subsequent reaction. Alternatively, it could be stored at −15 °C for several weeks without significant decomposition. The concentration of the azide was estimated based on the total volume of the solution and assuming a quantitative conversion based on the amount of triflic anhydride used.

Typical Procedure for the Preparation of the α-Diazo-α-nitro Carbonyl: Ethyl Nitrodiazoacetate (Table 1, entry 1). To a stirred solution of the ethyl nitroacetate (697 mg, 5.24 mmol) in acetonitrile (3 mL) under argon was added a 0.52 M solution of triflyl azide (11.1 mL, 5.76 mmol) in hexane. Pyridine (0.79 mL, 10.48 mmol) was then added dropwise (over ca. 3 min). The reaction mixture was stirred at room temperature for 15 h after which it was concentrated under reduced pressure (rotary evaporator). Purification of the crude residue by flash chromatography on silica gel ($CHCl_3$) afforded the pure nitrodiazo ester as a yellow oil (733 mg, 88%): R_f 0.55 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 101.7 (CN_2), 63.1, 14.2. IR (film) 2148, 1749, 1695, 1515 cm^{-1}.

Allyl Nitrodiazoacetate (Table 1, entry 2). The title compound was obtained as a yellow oil on a 1.07 mmol scale (88%) according to the general procedure: R_f 0.61 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.39 (m, 2H), 4.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 130.6, 120.1, 101.6 (CN_2), 67.1; IR (film) 2147, 1746, 1702, 1649, 1513 cm^{-1}.

Isopropyl Nitrodiazoacetate (Table 1, entry 3). The title compound was obtained as a yellow oil on a 1.08 mmol scale (90%) according to the typical procedure: R_f 0.67 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (sept, J = 5.7 Hz, 1H), 1.30 (d, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 101.6 (CN_2), 71.7, 21.8; IR (film) 2150, 1738, 1517, 1321, 1223, 1094, 908, 744 cm^{-1}.

(*E*)-Cinnamyl Nitrodiazoacetate (Table 1, entry 5). The title compound was obtained as a yellow crystalline solid on a 0.636 mmol scale (83%) according to the typical procedure: mp 62−63 °C; R_f 0.78 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.75 (d, J = 15.9 Hz, 1H), 6.30 (dt, J = 15.8, 6.7 Hz, 1H), 4.99 (d, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.8, 135.7, 128.9, 128.8, 127.0, 121.3, 67.6.; IR (film) 2145, 1738, 1699, 1515 cm^{-1}.

Cyclopropylmethyl Nitrodiazoacetate (Table 1, entry 6). This compound was obtained as a yellow oil on a 0.5 mmol scale (72%), according to the typical procedure: R_f 0.59 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, J = 7.4 Hz, 2 H), 1.20 (m, 1H), 0.64 (m, 2 H), 0.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 101.6 (CN_2), 71.8, 9.8, 3.6; IR (film) 2149, 1743, 1697, 1521 cm^{-1}.

4-(Benzyloxy)benzyl Nitrodiazoacetate (Table 1, entry 7). The title compound was obtained as a yellow crystalline solid on a 0.318 mmol scale (85%) according to the typical procedure: mp 89−90 °C; R_f 0.58 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 5.30 (s, 2H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 155.4, 136.8, 130.9, 128.8, 128.2, 127.6, 126.7, 115.2, 77.4 (CN_2), 70.2, 68.4; IR (film) 2146, 1745, 1694, 1612, 1514 cm^{-1}.

(1*R*,2*S*,5*R*)-Menthyl Nitrodiazoacetate (Table 1, entry 8). The title compound was obtained as a yellow oil on a 0.50 mmol scale (88%) according to the typical procedure: R_f 0.62 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (m, 1H), 2.08 (m, 1H), 1.84 (m, 1H), 1.72 (m, 2H), 1.51 (m, 2H), 1.10 (m, 2H), 0.92 (m, 6H), 0.86 (m, 1H), 0.79 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 101.6 (CN_2), 78.1, 47.1, 41.0, 34.1, 31.6, 26.6, 23.6, 22.1, 20.8, 16.5. IR (film) 2145, 1739, 1694, 1525 cm^{-1}. Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11. Found: C, 53.52; H, 7.38.

(1*R,2*S**)-2-Phenylcyclohexyl Nitrodiazoacetate (Table 1, entry 9).** This compound was obtained as a yellow oil on a 0.60 mmol scale (61%) according to the typical procedure: R_f 0.62 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.15 (m, 5H), 5.10 (m, 1H), 2.71 (m, 1H), 2.28 (m, 1H), 2.01−1.91 (m, 2H), 1.82 (m, 1H), 1.62 (m, 1H), 1.57−1.50 (m, 2H), 1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 142.3, 128.8, 127.5, 127.1, 101.1 (CN_2), 80.2, 49.8, 33.5, 32.5, 25.7, 24.8. IR (film) 2145, 1743, 1696, 1602, 1520 cm^{-1}.

(14) For the preparation of α-nitroketones, see: (a) Zen, S.; Koyama, M.; Doto, S. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. VI, pp 797−799. (b) Baker, D. C.; Putt, S. R. *Synthesis* **1978**, 478−479.

(15) General experimental procedures are described in the Supporting Information.

(16) See ref 1a for a general discussion about the stability of diazo compounds and sulfonyl azides.

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Typical Procedure for the Preparation of α-Nitro-α-diazo Ketones: α-Nitro-α-diazomethyl Cyclohexyl Ketone (Table 1, entry 12). To a solution of α-nitromethyl cyclohexyl ketone (171 mg, 1.00 mmol) in acetonitrile (1.0 mL) was added a 0.65 M solution of triflyl azide (1.69 mL, 1.1 mmol) in hexane. Pyridine (0.15 mL, 2.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 3 h at which point the reaction mixture was concentrated under reduced pressure (rotary evaporator). Purification of the crude product by flash chromatography on silica gel ($CHCl_3$) afforded the desired pure nitrodiazo ketone as a white solid (133 mg, 67%): mp 62 °C; R_f 0.69 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (m, 1 H), 1.86 (m, 4 H), 1.75 (m, 1 H), 1.42 (m, 4 H), 1.25 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 112.1 (CN_2), 47.3, 28.4, 25.8, 25.6. IR (KBr) 2174, 1651, 1532 cm^{-1}.

Nitrodiazomethyl *tert*-Butyl Ketone (Table 1, entry 11). This compound was obtained as a yellow oil on a 1.06 mmol scale (65%) according to the typical procedure: R_f 0.77 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 44.8, 25.7. IR (film) 2160, 1686, 1651, 1517 cm^{-1}.

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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