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Trifluoromethanesulfonyl azide: an efficient reagent for the preparation of α-cyano-α-diazo carbonyls and an α-sulfonyl-α-diazo carbonyl

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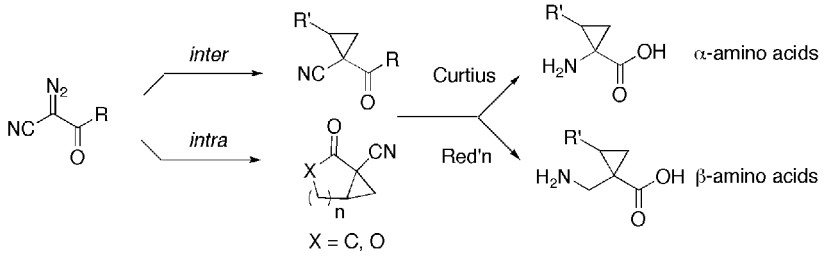
Abstract—The reaction scope of trifluoromethanesulfonyl azide in diazo transfer reactions was extended to include the preparation of α-cyano-α-diazo-carbonyls, phenyl sulfonyl diazoacetophenone and diethyl diazomalonate in high yields. The effect of the bases used in the diazo transfer reactions were found to have a dramatic influence on the success of the reaction with pyridine being the base of choice.

Our research group has been interested in the synthesis of cyclopropanes due to their presence in natural products and pharmaceutical candidates.[1] The transition metal-catalyzed cyclopropanation reaction involving diazo compounds and olefins, whether in intra- or intermolecular processes, represents a straightforward method for cyclopropane synthesis. Additionally, diazo compounds are ideal precursors for several other synthetically useful processes including C–H and X–H insertion reactions (X = O, N, S, P, Si, etc.)[2] and phosphorus or sulfur ylide formation.[3]

In our research program involving the asymmetric synthesis of unnatural amino acids,[4] we envisioned α-cyano-α-diazocarbonyl substrates as useful precursors to α-amino acids or β-amino acids containing a cyclopropane ring (Scheme 1). Introduction of the quaternary amine is often accomplished via Curtius or Hoffmann rearrangements[4a,5] while β-amino acids can be accessed through simple reduction of the nitrile.[6] More importantly, the cyano group is sterically small compared to nitro or ester groups, making discrimination during asymmetric catalysis potentially easier. Furthermore, α-cyano-α-diazo carbonyls have been shown to serve in a variety of other transformations including: bis(oxazole) syntheses,[7] O–H insertion reactions[8] and cyclopropanation reactions.[9] Herein, we report a simple and efficient method for the synthesis of α-cyano-α-diazocarbonyls using trifluoromethanesulfonyl (triflyl) azide and pyridine.[10,11] Finally, we highlight the unique and important aspect of using pyridine as the base in these diazo transfer reactions using triflyl azide as the reagent.



Scheme 1.

Keywords: diazo transfer; trifluoromethanesulfonyl azide; sulfonyl diazo carbonyl; cyano diazo sulfone.
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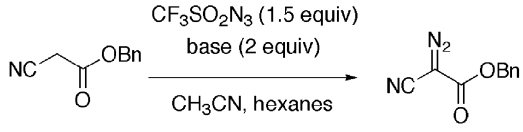
There exists a number of methods for the preparation of α-cyano-α-diazo carbonyl compounds including via a direct diazo transfer reaction[12] or via carbonyl cyanide hydrazones by treatment with oxidants such as $Pb(OAc)_4$ or Ag_2O, however, this method involves a more lengthy synthetic sequence.[8,13]

We reasoned that using a much more electrophilic azide, such as triflyl azide, in a direct diazo transfer reaction could also allow access to these types of diazo substrates. Its application would offer an attractive alternative to previously known methods due to its ease of preparation and handling (stored in solution). In our preliminary examination a variety of bases were screened in the diazo transfer reaction and the resulting reaction yields were found to be closely correlated to the pK_a (of the conjugate acid) of the base used (see Table 1).

Under the standard diazo transfer reaction conditions Hünig's base (i-Pr_2NEt) lead only to decomposition while weaker bases such as pyridine and 2,6-lutidine gave optimal yields of diazo substrate **2**. We then reasoned that the highly electrophilic diazo compound formed could be sensitive to the base. To test this hypothesis we treated the pure diazo compound **2** with two equivalents of Hünig's base under the diazo transfer conditions. The reaction color rapidly darkened and led to complete degradation of the diazo compound confirming our hypothesis. Inorganic bases such as potassium carbonate and sodium hydride were also tested and found to give good to excellent yields of diazo substrate **2**. In these cases the bases and their conjugate acids are non-nucleophilic allowing recovery of **2**. From these results, it appears that there is a good correlation between the pK_a (of the conjugate acid) of the base employed and the yield of the diazo transfer process for organic bases. Finally, pyridine was chosen for this diazo transfer reaction as the base of choice due to its simplicity of handling over sodium hydride.

Table 1. The influence of base on the yield of the diazo transfer reaction



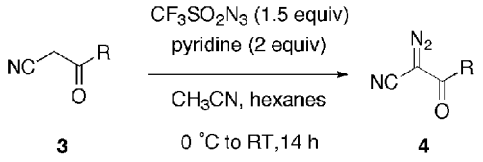
Entry	Base	pK_a Conjugate acid (H_2O)	Yield (%)
1	i-Pr_2NEt	ca. 11	Decomp.
2	DBU	ca. 12[a]	19
3	Et_3N	10.8	32
4	DMAP	9.2	53
5	Morpholine	8.4	48
6	4-Methyl morpholine	7.4	83
7	2,6-Lutidine	6.8	86
8	Pyridine	5.2	86
9	K_2CO_3	10.3	67
10	NaH	35[b,c]	86

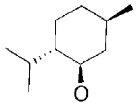
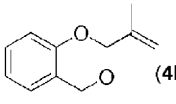
[a] Refers to the pK_a (of the conjugate acid) in DMSO.
[b] pK_a of hydrogen.
[c] Reaction performed in Et_2O.

The scope of the diazo transfer reaction was then examined. Treatment of ethyl cyano acetate with triflyl azide was found to cleanly transform the substrate to the corresponding diazo compound in high yield[14] (79%) noting that the corresponding diazo compound is slightly volatile (Table 2, entry 1). A variety of other cyano carbonyls[15] were tested and it was found that even bulky esters are also converted in reasonable yields (Table 2, entries 6 and 8). The reactions with α-cyanoketones (Table 2, entries 9 and 10) were found to be greatly accelerated due to their increased acidity and high yields were achieved in shorter reaction times using pyridine as a base.

Since the diazo transfer process is high yielding with α-nitrocarbonyl and α-cyanocarbonyl derivatives, we then wondered if other α-acidic substrates could also be transformed into the corresponding diazo compound under similar reaction conditions. When 2-(phenylsul-

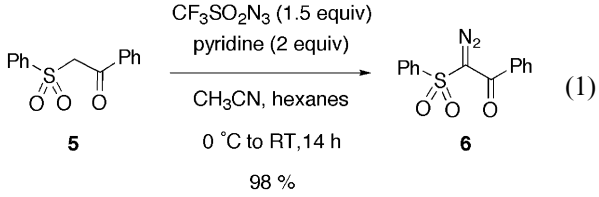
Table 2. Triflyl azide mediated diazo transfer with α-cyano carbonyls



Entry	R (Product)	Yield (%)[a]
1	OEt (**4a**)	79[b]
2	OCH_2CF_3 (**4b**)	81[b]
3	OPh (**4c**)	93
4	$OCH_2CH{=}CH_2$ (**4d**)	86
5	OBn (**4e**)	86
6	 (**4f**)	71[c]
7	(*Z*)-$OCH_2CH{=}CHCH_2CH_3$ (**4g**)	84
8	 (**4h**)	91
9	Ph (**4i**)	94
10	(*E*)-CH=CHPh (**4j**)	99

[a] Isolated yield after purification by flash chromatography.
[b] Product is volatile. [c] (1*R*, 2*S*, 5*R*)-(-)-Menthol.

fonyl) acetophenone **5** was treated with triflyl azide under the above reaction conditions, diazo substrate **6** was obtained in 98% yield (Eq. (1)). Additionally, diethyl malonate can also be prepared using this method in 51% and 56% isolated yields using K_2CO_3 and NaH respectively. The use of pyridine as a base resulted only in recovery of the starting material. In this case the irreversible nature of the deprotonation appears to be beneficial in cases of less acidic substrates.



(1)

In conclusion, we have extended the application of triflyl azide in diazo transfer reactions to the synthesis of α-cyano-α-diazo-carbonyls, phenyl sulfonyl diazoacetophenone and diethyl diazomalonate. We are currently investigating their applications in transition metal-catalyzed processes and the results of this research will be reported in due course.

Acknowledgements

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14. **General procedure for diazo transfer: ethyl cyanodiazoacetate (4a).** To a stirred solution of ethyl cyanoacetate (100 mg, 0.88 mmol) in acetonitrile (2.0 mL) cooled to 0°C was added triflyl azide[10] (1.6 mL, 0.85 M in hexane, 1.5 equiv.). Pyridine (0.14 mL, 1.76 mmol, 2 equiv.) was then added slowly dropwise. The reaction mixture was allowed to stir for 14 h, warming to room temperature, then concentrated under reduced pressure. Purification on silica gel ($CHCl_3$) afforded ethyl cyanodiazoacetate[13] as a volatile yellow oil (97 mg, 79%): R_f 0.46 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (q, $J=7.1$ Hz, 2H), 1.32 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 107.5, 76.8, 63.6, 14.4; IR (film) 2230 (CN), 2132 (CN_2), 1715 (C=O), 1294, 1246, 1135, 1013, 739 cm^{-1}. **2,2,2-Trifluoroethyl cyanodiazoacetate (4b).** Volatile yellow oil (116 mg, 81%): R_f 0.51 ($CHCl_3$); ^{19}F NMR (400 MHz, $CDCl_3$) δ −76.7 (t, $J=7.9$ Hz, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61–4.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 122.4 (q, $J=277.5$ Hz, 1C), 106.4, 61.8 (q, $J=37.6$ Hz, 1C), 51.9 (CN_2); IR (film) 2234 (CN), 2141 (CN_2), 1729 (C=O), 1417, 1323, 1172, 1127, 971 cm^{-1}; HRMS

(EI)$^+$: 193.009605 ($C_5H_2N_3O_2F_3$ calc. 193.009911). **Phenyl cyanodiazoacetate (4c).** Yellow solid (108 mg, 93%): Mp 70–71°C; R_f 0.36 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.43 (m, 2H), 7.27–7.31 (m, 1H), 7.16–7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.9, 129.7, 126.8, 121.2, 107.0, 52.0; IR (film) 2231 (CN), 2140 (CN_2), 1731 (C=O), 1493, 1325, 1301, 1191, 1088 cm^{-1}. Anal. calc. for $C_9H_5N_3O_2$: C 57.76, H 2.69, N 22.45; found: C 57.63, H 2.58, N 22.50. **Allyl cyanodiazoacetate (4d).** Yellow oil (91 mg, 86%): R_f 0.49 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.94 (m, 1H), 5.27–5.38 (m, 2H), 4.74 (dt, $J=5.9$, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 130.8, 119.9, 107.3, 67.6; IR (film) 2230 (CN), 2134 (CN_2), 1717 (C=O), 1368, 1133, 739 cm^{-1}. **Benzyl cyanodiazoacetate (4e).** Pale pink solid (99 mg, 86%): Mp 37–38°C; R_f 0.41 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.5, 129.0, 128.8, 128.6, 107.3, 68.7; IR (film) 2231 (CN), 2135 (CN_2), 1706 (C=O), 1379, 1316, 1116 cm^{-1}. **(1*R*,2*S*,5*R*)-Menthyl cyanodiazoacetate (4f).** Yellow oil (102 mg, 71%): $[\alpha]_D$ −92.9° (*c* 0.62, $CHCl_3$); R_f 0.59 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80–4.87 (m, 1H), 2.01–2.04 (m, 1H), 1.81–1.85 (m, 1H), 1.67–1.72 (m, 2H), 1.42–1.51 (m, 2H), 1.04–1.12 (m, 2H), 0.83–0.92 (m, 7H), 0.78 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 107.6, 78.4, 47.0, 41.0, 34.1, 31.6, 26.6, 23.7, 22.1, 20.8, 16.6; IR (film) 2229 (CN), 2130 (CN_2), 1706 (C=O), 1456, 1240, 1127, 950, 737 cm^{-1}. **(*Z*)-Pent-2-enyl cyanodiazoacetate (4g).** Yellow oil (392 mg, 84%): R_f 0.55 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62–5.71 (m, 1H), 5.41–5.49 (m, 1H), 4.76 (d, $J=6.7$ Hz, 2H), 2.06–2.11 (m, 2H), 0.93–0.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 138.6, 121.2, 107.4, 62.6, 20.8, 13.9; IR (film) 2229 (CN), 2132 (CN_2), 1713 (C=O), 1265, 1124, 918 cm^{-1}. **2-(2-Methyl-allyloxy)-benzyl cyanodiazoacetate (4h).** Yellow oil (382 mg, 91%): R_f 0.40 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.35 (m, 2H), 6.96 (t, $J=7.5$ Hz, 1H), 6.89 (d, $J=8.6$ Hz, 1H), 5.39 (s, 2H), 5.05 (d, $J=24.5$ Hz, 2H), 4.48 (s, 2H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 157.0, 140.7, 130.5, 123.0, 120.7, 112.8, 111.9, 107.4, 71.9, 64.7, 19.5; IR (film) 2229 (CN), 2131 (CN_2), 1717 (CO), 1495, 1243, 1126 cm^{-1}. Anal. calc. for $C_{14}H_{13}N_3O_3$: C 61.99, H 4.83, N 15.49; found: C 62.02, H 5.03, N 15.38. **Cyanodiazomethyl phenyl ketone (4i).** Yellow solid (112 mg, 94%): Mp 39–40°C; R_f 0.49 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.89 (m, 2H), 7.60–7.64 (m, 1H), 7.48–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 134.7, 134.0, 129.0, 128.2, 109.4; IR (solid) 2223 (CN), 2134 (CN_2), 1646 (C=O), 1281, 1247, 633 cm^{-1}. **Cyanodiazomethyl (*E*)-cinnamyl ketone (4j).** Pale pink solid (120 mg, 99%): Mp 108–109°C; R_f 0.41 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J=15.5$ Hz, 1H), 7.58–7.60 (m, 2H), 7.39–7.44 (m, 3H), 6.98 (d, $J=15.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 145.5, 133.6, 131.6, 129.2, 129.1, 118.7, 108.7, 59.0 (CN_2); IR (film) 2224 (CN), 2143 (CN_2), 1649 (C=O), 1592, 1339, 1197, 989, 574 cm^{-1}. Anal. calc. for $C_{11}H_7N_3O$: C 67.00, H 3.58, N 21.31; found: C 66.91, H 3.53, N 21.13. **2-(Phenyl sulfonyl) diazoacetophenone (6).** Pale yellow solid (174 mg, 98%): Mp 114–115°C; R_f 0.57 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–8.07 (m, 2H), 7.61–7.66 (m, 1H), 7.51–7.56 (m, 5H), 7.38–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 141.4, 135.8, 134.3, 133.2, 129.2, 129.0, 128.2, 127.5, 83.3 (CN_2); IR (film) 2114 (CN_2), 1633 (C=O), 1449, 1328, 1143 cm^{-1}. Anal. calc. for $C_{14}H_{10}N_2S_1O_3$: C 58.73, H 3.52, N 9.78; found: C 58.40, H 3.38, N 9.93.

Procedure employing NaH as a base: NaH was rinsed with hexanes (2×10 mL) and suspended in dry diethyl ether (2.5 mL) while cooling to 0°C. Benzyl cyanoacetate (100 mg, 0.57 mmol) in diethyl ether (2.5 mL) was then added slowly dropwise to the NaH suspension, stirred 15 mins at 0°C, then 1 h at room temperature. The resulting suspension was then cooled to 0°C and triflyl azide[10] (1.0 mL, 0.85 M in hexane, 1.5 equiv.) was added slowly dropwise. The reaction mixture was allowed to stir for 14 h, warming to room temperature then filtered and concentrated under reduced pressure. Purification was achieved as above.

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