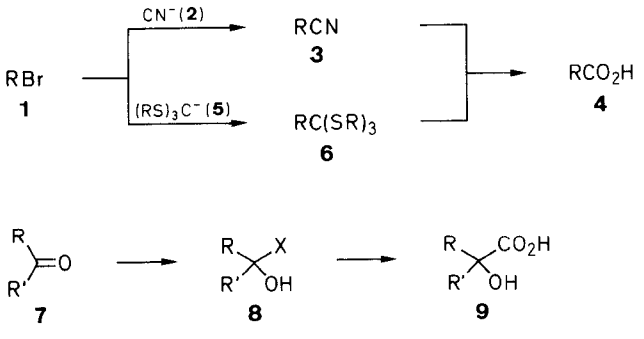
Tris(benzotriazol-1-yl)methane: A $^{-}CO_2H$ Synthon for the Preparation of Carboxylic Acids

Alan R. Katritzky,* Zhijun Yang, Jamshed N. Lam
Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

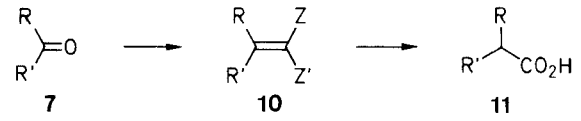
Lithiation of tris(benzotriazol-1-yl)methane **16** gives the tris(benzotriazolyl)methyl carbanion **17** which affords substitution products **18** with many electrophiles. Acidic hydrolysis of **18** affords the corresponding carboxylic acids **19** in good yield. The syntheses of several α-functionalized carboxylic acids are described.

The synthesis of carboxylic acids by carboxylation has relied on a variety of masked formyl anion equivalents.[1] The most common of these is cyanide which affords acids by reactions of type **1** to **4** (Scheme **A**). The preparation of α-hydroxy acids **9** from aldehydes and ketones **7** is often carried out via cyanohydrins **8** (X = CN).

Seebach[2] and Woessner[3] have treated the lithio salts of orthothioformates **5** with alkyl halides, or with carbonyl compounds, to afford adducts **6** and **8** (X = $C(SR)_3$) respectively, in good yield. Tris(phenylthio)methane[4] and other tris(alkylthio)[5] derivatives have also been employed, but few reports concern the synthetic utility of these derivatives as carboxylic acid[2] or ester[6] synthons.

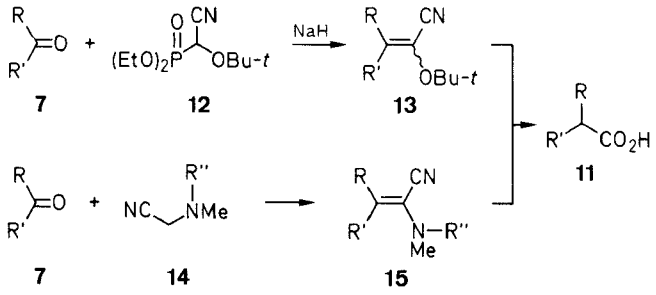


Scheme **A**



Scheme **B**

Carbonyl compounds have been converted into intermediates of type **10**, which on hydrolysis of both Z and Z' give acids (Scheme **B**). Examples of intermediates of this type are; (i) ketene thioacetals[7] **10** (Z,Z' = SR), (ii) α,β-unsaturated sulfones[8] **10** (Z = SO_2Ar, Z' = NHCHO), (iii) α,β-unsaturated phosphonates[9] **10** (Z = $PO(OEt)_2$, Z' = NMe_2), (iv) metalated trihalomethanes,[10–14] (v) a Horner–Emmons modification of the Wittig reaction using the reaction of diethyl *tert*-butoxy(cyano)methylphosphonate **(12)** with **7** to give α-*tert*-butoxyacrylonitriles **13** which, when converted to the acetoxy derivative, undergo basic solvolysis to form carboxylic acids,[15] (Scheme **C**) and (vi) aldehydes and benzophenone with [methyl(phenyl)amino]acetonitriles[16] **(14**, R'' = Ph) or aromatic aldehydes with methylamino- and dimethylaminoacetonitriles[17] **14** (R'' = H, R) give α-aminoacrylonitriles **15** which then undergo acid hydrolysis to form carboxylic acids (Scheme **C**).

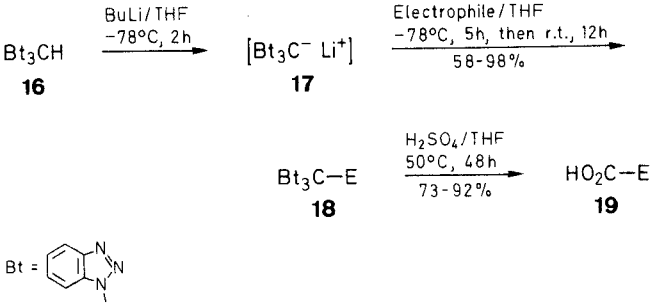


Scheme **C**

Many of these methods involve inefficient hydrolysis of the intermediates or difficult synthesis of starting materials. For instance cyanohydrins are obtained in low yields with certain aryl ketones.[18] The phosphonates **10** can be prepared only from aldehydes[9] and [aroyl(methyl)amino]acetonitriles **14** only from aromatic aldehydes.[17] Bromoform reacts only with aromatic aldehydes using a combination of potassium hydroxide and lithium chloride[10] or lithium amide[11] as catalyst. The thioacetals **10** (Z, Z' = SR) require the use of excess mercuric oxide and diethyl ether–boron trifluoride complex[5,19] for their hydrolysis to the carboxylic acids. Some α-alkoxyacrylonitriles[15] are difficult to hydrolyze. There is no general information as to the synthesis of α-aminoacrylonitriles.[16] Furthermore, in most cases only a few examples have been described, the generality of some of these systems is in doubt.

We now report a general procedure for the synthesis of carboxylic acids, which enables the introduction of various functional groups at the α-position (Scheme **D**).

The lithiation of **16** occurs readily with butyllithium in a solution of tetrahydrofuran at −78 °C to afford **17**.



Electrophile	18, 19	E
$PhCH_2Br$	**a**	$PhCH_2$
$PhCH{=}CHCH_2Br$	**b**	$PhCH{=}CHCH_2$
PhCOCl	**c**	PhCO
$4\text{-}CH_3C_6H_4COCl$	**d**	$4\text{-}CH_3C_6H_4CO$
$PhCHO/Me_3SiCl$	**e**	$PhCH(OSiMe_3)$
$4\text{-}CH_3C_6H_4CHO/Me_3SiCl$	**f**	$4\text{-}CH_3C_6H_4CH(OSiMe_3)$
BuI	**g**	Bu
PhNCS	**h**	PhNHCS
1-naphthylNCS	**i**	1-naphthylNHCS
$PhCH_2NCS$	**j**	$PhCH_2NHCS$
$CS_2/PhCH_2Br$	**k**	$PhCH_2SC(S)$
$ClCO_2Et$	**l**	CO_2Et

Scheme **D**

Table 1. Physical Data of Compounds **18** Prepared

Product	Yield (%)	mp (°C)	Crystal Form	Molecular Formula[a]
18a	92	120–122	microcrystals[b]	$C_{22}H_{19}N_9$ (409.4)
18b	84	145–147	plates[c]	$C_{28}H_{21}N_9$ (483.5)
18c	98	265–267	microcrystals[d]	$C_{26}H_{17}N_9O$ (471.4)
18d	98	263–265	microcrystals[e]	$C_{27}H_{19}N_9O$ (485.4)
18e	91	190–191	plates[b]	$C_{29}H_{27}N_9OSi$ (545.5)
18f	94	205–207	needles[b]	$C_{30}H_{29}N_9OSi$ (559.6)
18g	86	172–174	plates[b]	$C_{23}H_{21}N_9$ (423.4)
18h	90	200–201	plates[d]	$C_{26}H_{18}N_{10}S$ (502.4)
18i	89	205–207	plates[d]	$C_{30}H_{20}N_{10}S$ (552.5)
18j	80	195–197	plates[d]	$C_{27}H_{20}N_{10}S$ (516.5)
18k	58	162–164	microcrystals[f]	$C_{27}H_{19}N_9S_2$ (533.4)
18l	95	215–217	plates[g]	$C_{22}H_{17}N_9O_2$ (439.4)

[a] Satisfactory microanalyses obtained: C ±0.39, H ±0.11, N ±0.44.
[b] From MeOH.
[c] From EtOH.
[d] From acetone.
[e] From acetone/MeOH.
[f] Column chromatography ($CHCl_3$: hexanes 2 : 1).
[g] From EtOAc.

Interestingly while the anions from the mono-[20] and bis(benzotriazol-1-yl)methyl[21] derivatives are dark blue, derivative **17** is pale yellow. The anion **17** reacts with alkyl and acyl halides, isothiocyanates, and chloroformates to form the corresponding adducts **18** in high yield (Table 1). The reaction of **17** with 4-methylbenzaldehyde resulted in recovery of the starting material. However, when chlorotrimethylsilane was added to the reaction mixture (after addition of the 4-methylbenzaldehyde), the corresponding silyl ether **18f** was obtained in excellent yield. A similar pattern was also observed in the

Table 2. Spectroscopic Data of Compounds **18** Prepared

Product	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$)		
		$C_{quat.}$	Bt	E
18a	5.39 (s, 2H), 6.75–7.4 (m, 14H), 8.06 (d, 3H, J = 7.4)	94.1	112.4, 120.5, 124.9, 128.8, 132.6, 146.8	44.77, 128.28, 128.3, 130.6, 130.9
18b	4.81 (d, 1H, J = 7.1), 5.92 (d, 1H, J = 14.6), 6.2–6.4 (m, 1H), 6.8–6.9 (m, 2H), 7.08–7.15 (m, 6H), 7.3–7.4 (m, 6H), 8.0–8.1 (m, 3H)	92.9	111.8, 120.5, 125.0, 128.9, 132.2, 146.8	43.15, 118.9, 126.1, 127.8, 128.2, 135.6, 137.0
18c	6.9–7.0 (m, 3H), 7.15–7.4 (m, 9H), 7.7–7.75 (m, 2H), 8.0–8.05 (m, 3H)	91.04	111.4, 120.4, 125.3, 129.5, 133.2, 146.4	128.5, 129.9, 132.6, 134.6, 182.9
18d	2.21 (s, 3H), 6.9–7.0 (m, 5H), 7.2–7.35 (m, 6H), 7.62 (d, 2H, J = 8.5), 8.0–8.05 (m, 3H)	91.05	111.5, 120.3, 125.2, 129.4, 133.2, 146.4	21.6, 129.3, 130.1, 146.0, 182.3
18e	−0.21 (s, 9H), 6.9–7.0 (m, 4H), 7.1–7.4 (m, 10H), 7.81 (s, 1H), 8.0–8.1 (m, 3H)	96.0	113.8, 120.0, 124.8, 128.2, 133.0, 146.5	0.1, 78.7, 127.7, 128.9, 129.2, 135.5
18f	−0.22 (s, 9H), 2.17 (s, 3H), 6.7–6.8 (m, 4H), 7.1–7.4 (m, 9H), 7.83 (s, 1H), 7.9–8.1 (m, 3H)	96.1	113.8, 120.0, 124.7, 128.2, 133.0, 146.5	0.0, 21.0, 78.6, 128.4, 128.8, 132.4, 139.1
18g	0.78 (t, 3H, J = 7), 1.25–1.45 (m, 4H), 3.9–4.0 (m, 2H), 7.07–7.12 (m, 3H), 7.3–7.4 (m, 6H), 8.05–8.1 (m, 3H)	93.3	111.6, 120.4, 124.9, 128.9, 132.0, 146.6	13.4, 21.9, 25.4, 39.2
18h[a]	7.15–7.4 (bs, 1H), 7.9–8.15 (m, 14H), 8.75–8.8 (m, 3H)	93.2	112.0, 120.1, 124.7, 129.0, 134.0, 145.7	125.3, 127.7, 129.5, 138.7, 182.8
18i[a]	6.95–7.45 (m, 3H), 7.7–8.0 (m, 11H), 8.25–8.4 (m, 2H), 8.5–8.8 (m, 4H)	93.4	112.1, 120.2, 125.6, 129.6, 133.9, 145.8	123.7, 124.0, 125.4, 126.5, 126.6, 128.2, 128.5, 128.6, 134.0, 136.0, 185.7
18j[a]	5.0 (d, 2H, J = 5.4), 6.6–6.65 (m, 3H), 7.2–7.6 (m, 11H), 8.19 (m, 3H), 11.86 (m, 1H)	92.9	112.0, 120.0, 125.2, 128.4, 133.9, 145.7	51.3, 127.4, 128.1, 129.3, 135.9, 183.8
18k	6.74 (d, 3H, J = 8.3), 7.05–7.4 (m, 11H), 8.06 (d, 3H, J = 8.3)	95.8	112.2, 120.3, 125.1, 129.2, 132.6, 146.3	43.5, 128.6, 129.0, 129.4, 133.8, 214.7
18l	1.15 (t, 3H, J = 7.1), 4.51 (q, 2H, J = 7.1), 6.9–7.0 (m, 3H), 7.3–7.4 (m, 6H), 8.07–8.1 (m, 3H)	88.7	111.3, 120.4, 125.2, 129.3, 133.0, 146.5	13.5, 65.7, 160.9

[a] Solvent DMSO-d_6.

Table 3. Carboxylic Acids **19** Prepared

Product	Yield (%)	mp (°C) or bp (°C)/Torr	Lit. mp (°C) or bp (°C)/Torr
19a	92	76–77	76–76.5[23]
19b	73	85–86	87[24]
19c	81	62–64	61–64[25]
19d	83	94–95	91–93[25]
19e	78	117–118	115–117[26]
19f	76	144–145	145–145.5[27]
19g	79	85–87/15	80–83/10[28]
19h	82	95–96	–
19i	87	118–120	–
19j	74	oil	–

reaction of *p*-[bis(benzotriazol-1-yl)methyl]toluene with aldehydes.[21] However, probably for steric reasons, the anion **17** did not react with secondary halides or with ketones. With 2,2-dimethylpropanal, the reaction goes only to 10% completion.

The derivatives **18** were characterized by their CHN analysis and by their ^{1}H- and ^{13}C-NMR spectra. Absence of the methine signal at δ = 10.2 and 78.0, indicated complete reaction. The quaternary carbons were observed between δ = 88.7 and 96.1, those attached to an electron deficient carbon atom resonated at the higher field end of this range. Six resonances were observed for the benzotriazole carbon atoms indicating no isomerization to the 2-substituted derivatives.

Treatment of the benzylated derivative **18a** at room temperature with 1 M, 5 M, or 10 M hydrochloric acid in tetrahydrofuran yielded starting material only. When the reaction solution was heated under reflux for 72 h, a mixture, including the starting material, was obtained. However, with 95% sulfuric acid in tetrahydrofuran at 50 °C for 48 h, hydrolysis of **18a** occurred smoothly: benzotriazole hydrogen sulfate precipitated and phenylacetic acid was obtained in 92% yield. Under similar conditions the corresponding α-keto, α-hydroxy, and other α-functionalized carboxylic acids were obtained in good yields: all are known compounds except the arylaminothioxoacetic acids **19h–j**.

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H-NMR spectra (300 MHz) were recorded on a Varian VXR-300 spectrometer with TMS as internal reference. ^{13}C-NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ = 77.0 or DMSO-d_6, δ = 39.5) as references. Microanalyses were obtained using a Carlo Erba 1106 elemental analyzer under the supervision of Dr. D. Powell, University of Florida. THF was freshly distilled from Na/benzophenone. All moisture sensitive reactions were carried out in a dry Ar atmosphere.

Tris(benzotriazol-1-yl)methane (16):
A mixture of benzotriazole (119 g, 1.0 mol), aq NaOH (40%, 100 mL), and Bu_4NBr (3.2 g) in $CHCl_3$ (100 mL) is heated under reflux for 48 h. The reaction mixture is cooled and the organic

material extracted with $CHCl_3$ (2 × 100 mL). The organic layer is washed with H_2O (5 × 25 mL), dried ($MgSO_4$) and concentrated at reduced pressure to give a brown solid. Trituration with MeOH affords the pure product; yield: 60.5 g (50%); mp 194–196°C (Lit.[22] mp 191°C).

Lithiation of Tris(benzotriazol-1-yl)methane (16) and Reaction with Electrophiles; General Procedure:

BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) is added dropwise at −78°C to a solution of tris(benzotriazol-1-yl)methane (**16**; 3.67 g, 10 mmol) in dry THF (80 mL). The mixture is stirred at −78°C for 2 h, and then the corresponding electrophile (11 mmol) in THF (10 mL) is added (for the silyl derivatives **18e,f**, a solution of Me_3SiCl (11 mmol) in THF (10 mL) is added to the above solution 30 mins after adding the aldehyde). The mixture is stirred at −78°C for 5 h, and then at r.t. for 12 h. The reaction mixture is poured into sat. aq NH_4Cl (40 mL), and the aq layer extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers are washed with H_2O (1 × 25 mL), dried, ($MgSO_4$) and the solvent removed at reduced pressure to afford the crude adducts which are then recrystallized to give analytically pure products **18a–18l** (Tables 1 and 2).

Hydrolysis of Compounds 18a–18j; General Procedure:

To a stirred solution of the trisbenzotriazolyl derivative (**18**; 2 mmol) in THF (20 mL) is added conc. H_2SO_4 (95–98%, 0.5 mL) and the solution stirred at 50°C for 48 h. Benzotriazole is filtered off and the filtrate evaporated at reduced pressure to give an oil. H_2O (5 mL) is added and the mixture extracted with Et_2O (3 × 10 mL). The combined extracts are washed with cold H_2O (2 × 5 mL), and dried ($MgSO_4$). Evaporation of the solvent gives the crude products which are then purified accordingly to afford the carboxylic acids **19a–19j** (Table 3).

Phenylaminothioxoacetic Acid (**19h**):

Yellow needles (cyclohexane); yield: 0.30 g (82%); mp 95–96°C.

$C_8H_7NO_2S$ calc. C 53.04 H 3.87 N 7.73
found 53.02 3.84 7.73

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.3–7.5 (m, 3H), 7.8–8.0 (m, 2H), 10.86 (s, 1H).

^{13}C-NMR ($CDCl_3$): δ = 121.5, 128.1, 129.3, 137.1, 158.5, 178.0.

1-Naphthylaminothioxoacetic Acid (**19i**):

Yellow needles (cyclohexane); yield: 0.40 g (87%); mp 118–120°C.

$C_{12}H_9NO_2S$ calc. C 62.34 H 3.90 N 6.06
found 62.58 4.00 5.95

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.5–7.9 (m, 7H), 8.28–8.32 (m, 1H), 11.19 (s, 1H).

^{13}C-NMR ($CDCl_3$): δ = 120.1, 121.1, 125.2, 126.7, 126.9, 127.4, 128.9, 129.0, 132.2, 134.0, 158.5, 180.4.

Benzylaminothioxoacetic Acid (**19j**):

Yellow oil; yield: 0.29 g (74%).

HRMS: *m/z*, $C_9H_9NO_2S$ (M^+) calc.: 195.0354; found 195.0358.

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.72 (d, 2H, J = 6 Hz), 7.27 (s, 5H), 9.50 (bs, 1H), 9.65 (bs, 1H).

^{13}C-NMR ($CDCl_3$): δ = 50.6, 128.0, 128.1, 128.6, 134.1, 158.0, 182.5.

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