Efficient Transformations of Aldehydes and Ketones into One-Carbon Homologated Carboxylic Acids

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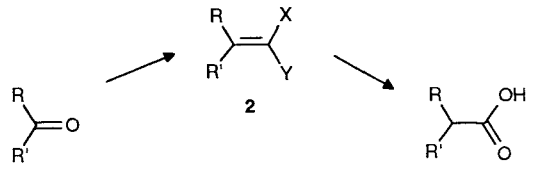
Peterson olefination of aldehydes and ketones with trimethylsilyl(methoxy)(benzotriazol-1-yl)methyl anion **6** afforded 1-(benzotriazol-1-yl)-1-methoxyalk-1-enes **7** which were treated without isolation with zinc bromide and hydrochloric acid, to yield the corresponding one-carbon homologated carboxylic acids **4** in good overall yields.

Synthetic transformations of carbonyl compounds **1** into one-carbon homologated carboxylic acids **4** (Scheme 1) are of great importance as evidenced by the volume of literature on this subject.[1-14] The most important and most commonly used methods for the transformation **1** → **4** rely on the hydrolysis of intermediates of type **2** as shown by the following classification:



Scheme 1

(i) α-Acetoxyacrylonitriles (**2**, X = OAc, Y = CN) are prepared from the reactions of diethyl *tert*-butoxy(cyano)methylphosphonate $(EtO)_2POCH(CN)OBu^t$ with aldehydes and ketones, followed by the replacement of the *tert*-butyl group by the acetyl group,[9] or from the reaction of chloroacetonitrile with ketones, followed by the treatment with anhydrous HCl and acetic anhydride.[7] However, both processes require three steps for the transformations of ketones to acids and involve manipulation of toxic cyanides.

(ii) α-Cyanoenamines (**2**, X = PhNMe or NMe_2, Y = CN) are obtained from the reactions of α-(*N*-methylamino)acetonitrile[12] or $Me_2NCH(CN)PO(OEt)_2$[11] with carbonyl compounds. However, this method may not be general for ketones, for which benzophenone[12] and acetophenone[11] are the only examples reported. Moreover, the whole transformation **1** → **4** requires two steps.

(iii) α-Cyanoenamides (**2**, X = ArCONMe, Y = CN) are produced from α-(*N*-aroyl-*N*-methylamino)acetonitriles and carbonyl compounds.[13] However, this approach is apparently limited to aromatic aldehydes.

(iv) α-Phosphonoenamines (**2**, X = $PO(OEt)_2$, Y = NMe_2) are prepared from *N*,*N*-dimethylaminomethylenediphosphonate $Me_2NCH[PO(OEt)_2]_2$ and aldehydes.[3,10] However, the reported yields from the application of this method to non-conjugated aldehydes are less than 35%.[10]

(v) 1-Formylamino-1-sulfonylalkenes (**2**, X = NHCO, Y = SO_2Ar) are obtained from the reactions of aldehydes and ketones with aryl isocyanomethyl sulfones $CNCH_2SO_2Ar$.[5] However, two steps are required to transform **1** → **4** in overall yields of 35–50%.

(vi) Ketene thioacetals [**2**, X, Y = $S(CH_2)_3S$] are prepared from the reactions of 2-trimethylsilyl-1,3-dithian[6] or 1,3-dithiacyclohexylidinetrimethoxyphosphorane[2] with aldehydes and ketones. However, effective hydrolysis for these approaches involves the use of mercury salts.

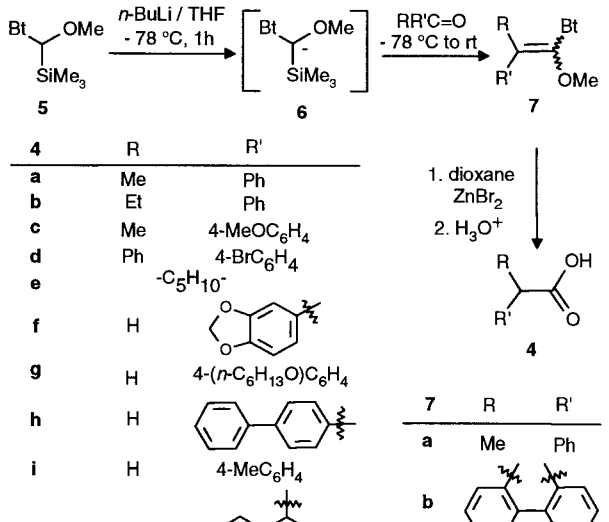
(vii) Ketene-*O*,*S*-acetals (**2**, X = OMe, Y = SPh),[15] produced from the Peterson olefination of methoxyphenylthiotrimethylsilylmethane with aldehydes and ketones, are readily converted into thioesters on treatment with TMSCl, NaI or with LiSMe. This strategy is of potential utility for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids.

Alternative approaches for the transformation **1** → **4** involve the intermediates **3** (Scheme 1) from the addition of cyanide to carbonyl compounds. Accordingly, aldehydes or aryl methyl ketones react with cyanide, followed by *O*-acetylation, deacetoxylation by catalytic hydrogenation, and hydrolysis of the cyano group to afford one-carbon homologated carboxylic acids.[1,8,14] Other routes are via cyanoepoxides.[7] However, these processes are multistep and use cyanides.

We have recently demonstrated the utility of alkoxy(benzotriazol-1-yl)methanes as versatile one-carbon homologation reagents.[16-18] Their silylated derivatives, trimethylsilyl(alkoxy)benzotriazol-1-ylmethanes have been used by Johnson et al. in facile synthesis of oxindoles via Peterson olefination and photolysis.[19,20] We have now developed trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** and demonstrated that it provides a convenient method for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids.

Trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** was easily prepared in 75% yield as a crystalline solid by our previously reported method.[21] The lithiation of **5** occurred readily with butyllithium at −78 °C to give a deep blue solution of the anion **6**, which underwent Peterson olefination reactions with acetophenone and fluorenone to give 1-(1-methoxyalk-1-enyl)benzotriazoles **7a** and **7b** respectively in 76% and 81% yields. Compound **7a** was obtained as a mixture of *cis*- and *trans*-isomers (Scheme 2). The 1-(1-methoxyalk-1-enyl)-benzotriazole is equivalent synthetically to an acylbenzotriazole synthon in which the carbonyl group is masked as an enol ether. Accordingly, transformation of **7** into

carboxylic acids was readily achieved in excellent yield by treatment with zinc bromide and hydrochloric acid in refluxing 1,4-dioxane, as exemplified by the conversion of **7a** into the corresponding acid **4a** (for reviews of benzotriazole as a leaving group, see refs. 16, 22–24).



Scheme 2

Conveniently, it is not necessary to separate the intermediates **7** for the preparation of carboxylic acids **4**. Thus, trimethylsilyl(methoxy)benzotriazol-1-ylmethyl anion **6** was treated with a variety of aldehydes and ketones (Scheme 2), and the resulting crude intermediates **7** were subjected to hydrolysis with hydrochloric acid in the presence of zinc bromide to provide the corresponding one-carbon homologated acids **4b–k** in 45–57% overall yields from the starting aldehydes and ketones. Byproduct benzotriazole was easily removed due to its lower acidity (see experimental section). As shown in Scheme 2, this approach works well with both aliphatic and aromatic aldehydes and aryl aryl, alkyl aryl and alkyl alkyl ketones, demonstrating its wide generality.

1-(1-Methoxyalk-1-enyl)benzotriazoles **7a** and **7b**, and carboxylic acids **4a–k** all showed the expected ^1H and ^{13}C spectra and all new compounds were further characterized by their elemental analyses.

In summary, trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** is an advantageous reagent for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids in light of the generality of the method, the ready availability of the starting materials and the simplicity of the experimental procedure.

Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were recorded using $CDCl_3$ as the solvent with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). THF was distilled under N_2 immediately prior to use from Na/benzophenone. All reactions with air-sensitive compounds were carried out under Ar. Column chromatography was conducted with silica gel 230–400 mesh. Trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** was prepared according to our reported procedure.[21]

1-(Benzotriazol-1-yl)-1-methoxyalk-1-enes 7a and 7b; General Procedure:

To a solution of trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** (1.17 g, 5 mmol) in THF (70 mL) at −78 °C under Ar was added BuLi (2.9 mL, 5.7 mmol, 2 M in cyclohexane). After 1 h, the appropriate ketone (5.7 mmol) in THF (8 mL) was added. The mixture was stirred at −78 °C for an additional hour and warmed to r.t. overnight. Sat aq NH_4Cl (70 mL) was added and the mixture extracted with Et_2O (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography.

1-(Benzotriazol-1-yl)-1-methoxy-2-phenylprop-1-ene **(7a)**:
Hexane/Et_2O (4 : 1) as eluent gave a mixture of *cis*- and *trans*-isomers; yield: 1.15 g (76%). For characterization purposes, this oil mixture was recrystallized from hexane/Et_2O to give the *trans*-isomer; yield: 0.46 g (35%); mp 101–102 °C.

^1H NMR: δ = 2.35 (s, 3H), 3.41 (s, 3H), 6.91–6.99 (m, 5H), 7.25–7.30 (m, 1H), 7.35–7.37 (m, 2H), 7.96 (d, J = 8.2 Hz, 1H).

^{13}C NMR: δ = 17.5, 57.0, 110.0, 119.7, 120.0, 124.0, 127.0, 127.2, 128.0, 128.1, 133.2, 137.9, 139.3, 144.9.

$C_{16}H_{15}N_3O$	calc.	C 72.42	H 5.70	N 15.84
(265.3)	found	72.41	5.59	16.02

Fluorenylidene(methoxy)benzotriazol-1-ylmethane **(7b)**:
Hexane/Et_2O (3 : 1) as eluent gave pure **7b**; yield: 1.1 g (81%); mp 134–136 °C.

^1H NMR: δ = 3.59 (s, 3H), 5.50 (d, J = 7.9 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 6.6 Hz, 1H), 7.40–7.55 (m, 5H), 7.68 (d, J = 7.6 Hz, 1H), 7.75–7.78 (m, 1H), 8.24–8.29 (m, 2H).

^{13}C NMR: δ = 56.3, 110.2, 118.3, 119.6, 119.7, 120.4, 122.4, 125.1, 125.5, 127.0, 127.4, 127.7, 128.4, 129.4, 133.1, 134.6, 136.1, 139.6, 139.7, 140.7, 145.5.

$C_{21}H_{15}N_3O$	calc.	C 77.52	H 4.65	N 12.91
(325.3)	found	77.53	4.49	12.94

2-Phenylpropionic Acid (4a) from Intermediate Product 7a:

To a solution of 1-(benzotriazol-1-yl)-1-methoxy-2-phenylprop-1-ene **(7a)** (0.26 g, 1 mmol) in anhyd 1,4-dioxane (5 mL) under Ar was added $ZnBr_2$ (0.56 g, 2.5 mmol). After the mixture was refluxed for 1 h, aq HCl (1 mL, 6 M) was added. The mixture was further refluxed for 4 h. The solvent was evaporated at reduced pressure and H_2O (20 mL) was added to the residue. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was extracted with aq $NaHCO_3$ (3 × 20 mL, 5%). The aqueous layer was acidified with HCl (6 M) to pH = 4 and extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with H_2O (20 mL), dried ($MgSO_4$) and evaporated to give the pure oil (Lit.[25] bp 177 °C/44 mm); yield: 0.12 g (80%).

^1H NMR: δ = 1.50 (d, J = 7.2 Hz, 3H), 3.73 (q, J = 7.2 Hz, 1H), 7.25–7.32 (m, 5H), 12.01 (br s, 1H).

^{13}C NMR: δ = 18.1, 45.4, 127.4, 127.6, 128.7, 139.7, 180.9.

Carboxylic Acids 4b–h from Aldehydes and Ketones; General Procedure:

To a solution of trimethylsilyl(methoxy)benzotriazol-1-ylmethane **(5)** (1.17 g, 5 mol) in THF (70 mL) at −78 °C under Ar was added BuLi (2.9 mL, 5.7 mmol, 2 M in cyclohexane). After 1 h, the appropriate ketone or aldehyde (5.7 mmol) in THF (8 mL) was added. The mixture was stirred at −78 °C for an additional hour and warmed to r.t. overnight. Sat aq NH_4Cl (70 mL) was added and the mixture extracted with Et_2O (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was passed through a Buchner funnel filled with silica gel. The Et_2O was removed from the filtrate and the residue dissolved in anhyd 1,4-dioxane (20 mL). To this solution under Ar was added $ZnBr_2$ (1.42 g, 6.3 mmol). After the mixture was refluxed for 1 h, aq HCl (2.5 mL, 6 M) was added. The mixture was further refluxed for 4 h. The solvent was evaporated at reduced pressure and H_2O (50 mL) was added to the residue.

The mixture was extracted with Et_2O (3 × 50 mL). The combined organic layer was extracted with aq $NaHCO_3$ (3 × 50 mL, 5%). The aqueous layer was acidified with HCl (6 M) to pH = 4 and extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with H_2O (60 mL), dried ($MgSO_4$) and evaporated to give the pure product.

Phenylbutyric Acid **(4b):**
colorless solid; yield: 0.45 g (55%); mp 39–42°C (Lit.[26] mp 42–43°C).

^{1}H NMR: δ = 0.90 (t, J = 7.4 Hz, 3H), 1.73–1.88 (m, 1H), 2.03–217 (m, 1H), 3.45 (t, J = 7.7 Hz, 1H), 7.22–7.32 (m, 5H), 10.98 (br s, 1H).

^{13}C NMR: δ = 12.1, 26.3, 53.4, 127.4, 128.1, 128.6, 138.3, 180.5.

2-(4-Methoxyphenyl)propionic Acid **(4c):**
colorless solid; yield: 0.48 g (53%); mp 54–45°C (Lit.[27] mp 56–57°C).

^{1}H NMR: δ = 1.48 (d, J = 7.2 Hz, 3H), 3.68 (q, J = 7.2 Hz, 1H), 3.77 (s, 3H), 6.85 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 10.50 (br s, 1H).

^{13}C NMR: δ = 18.1, 44.5, 55.2, 114.0, 128.6, 131.9, 158.8, 181.0.

α-(4-Bromophenyl)phenylacetic Acid **(4d):**
colorless solid; yield: 0.63 g (43%); mp 118–120°C (Lit.[28] mp 120–121°C).

^{1}H NMR: δ = 4.99 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.28–7.33 (m, 5H), 7.44 (d, J = 8.5 Hz, 2H), 11.38 (br s, 1H).

^{13}C NMR: δ = 56.4, 121.6, 127.7, 128.5, 128.8, 130.4, 131.7, 136.8, 137.3, 178.5.

Cyclohexylformic Acid **(4e):**
colorless oil (Lit.[29] bp 63–67°C/1 mm); yield: 0.36 g (55%).

^{1}H NMR: δ = 1.20–1.96 (m, 10H), 2.28–2.38 (m, 1H), 11.83 (br s, 1H).

^{13}C NMR: δ = 25.2, 25.6, 28.7, 42.9; 182.7.

3,4-Methylenedioxyphenylacetic Acid **(4f):**
colorless solid; yield: 0.51 g (57%); mp 125–127°C (Lit.[30] mp 127°C).

^{1}H NMR: δ = 3.55 (s, 2H), 5.94 (s, 2H), 6.69–6.77 (m, 3H) (OH signal was not detected).

^{13}C NMR: δ = 42.2, 102.7, 109.9, 111.4, 124.1, 128.3, 148.5, 149.4, 179.4.

(4-Hexyloxyphenyl)acetic Acid **(4g):**
colorless solid; yield: 0.53 g (45%); mp 80–81°C (Lit.[31] mp 77–78.5°C).

^{1}H NMR: δ = 0.90 (t, J = 6.8 Hz, 3H), 1.29–1.35 (m, 4H), 1.40–1.50 (m, 2H), 1.71–1.81 (m, 2H), 3.57 (s, 2H), 3.93 (t, J = 6.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 9.85 (br s, 1H).

^{13}C NMR: δ = 15.6, 24.2, 27.3, 30.8, 33.2, 41.8, 69.6, 116.3, 126.7, 131.9, 160.0, 179.9.

(4-Phenyl)phenylacetic Acid **(4h)**:
colorless solid; yield: 0.48 g (45%); mp 162–164°C (Lit.[32] mp 153°C).

^{1}H NMR: δ = 3.70 (s, 2H), 7.34–7.46 (m, 5H), 7.55–7.59 (m, 4H), 10.40 (br s, 1H).

^{13}C NMR: δ = 40.7, 127.1, 127.3, 127.4, 128,8, 129.8, 132.2, 140.4, 140.7, 177.8.

$C_{14}H_{12}O_2$	calc.	C 79.23	H 5.70
(212.1)	found	79.02	5.78

(4-Methylphenyl)acetic Acid **(4i):**
colorless solid; yield: 0.42 g (56%); mp 90–92°C (Lit.[33] mp 87–91.5°C).

^{1}H NMR: δ = 2.33 (s, 3H), 3.60 (s, 2H), 7.11–7.18 (m, 4H), 10.62 (br s, 1H).

^{13}C NMR: δ = 21,0, 40.6, 129.2, 129.3, 130.2, 137,0, 178.2.

1-Naphthylacetic Acid **(4j):**
colorless solid; yield: 0.53 g (57%); mp 130–132°C (Lit.[34] mp 132°C).

^{1}H NMR: δ = 4.07 (s, 2H), 7.38–7.55 (m, 4H), 7.78–7.87 (m, 2H), 7.95 (d, J = 8.9 Hz, 1H), 10.40 (br s, 1H).

^{13}C NMR: δ = 38.7, 123.6, 125.4, 125.8, 126.5, 128.2, 128.3, 128.7, 129.7, 132.0, 133.8, 178.1.

3-Phenylbutanoic Acid **(4k):**
colorless oil (Lit.[35] bp 142°C/1mm); yield: 0.44 g (54%).

^{1}H NMR: δ = 1.33 (d, J = 7.0 Hz, 3H), 2.55–2.73 (m, 2H), 3.22–3.34 (m, 1H), 7.22–7.35 (m, 5H), 11.31 (br s, 1H).

^{13}C NMR: δ = 21.8, 36.1, 42.6, 126.5, 126.7, 128.5, 145.4, 178.8.

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