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3-Benzyloxy-1-isocyanopropenes. Synthesis and Use as 3-Hydroxypropanoyl Anion Equivalents

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Abstract: New acyl anion equivalents bearing a hydroxyl group at the β-position have been developed. Treatment of 3-benzyloxy-1-isocyanopropenes with lithium diisopropylamide (LDA) in THF at -78 °C generated the 1-lithio compounds, which reacted with alkyl halides to afford the corresponding 1-alkylated products in good yields. Acid hydrolysis of these alkylated products followed by hydrogenolysis of the resulting β-benzyloxyethyl ketones led to β-hydroxyethyl ketones.

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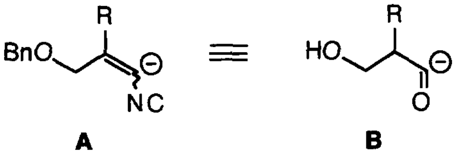
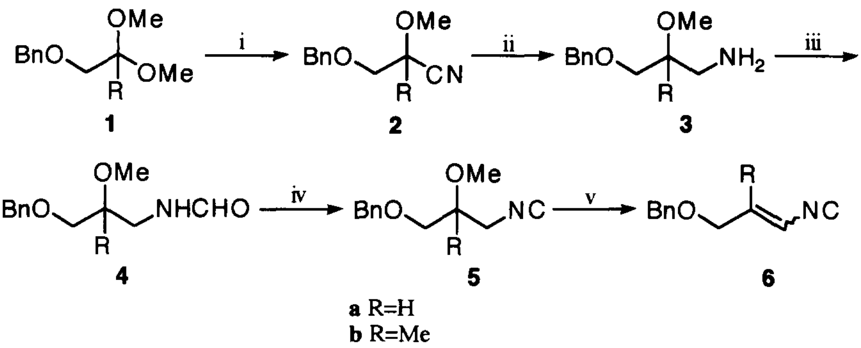
Although the successful use of metallated organic compounds as acyl anion equivalents has been reported,[1] surprisingly only a few acyl anion equivalents bearing a functional group have been developed.[2] In this paper we wish to report that 3-benzyloxy-1-isocyano-1-propenyl anions (**A**) generated from the deprotonation of 3-benzyloxy-1-isocyanopropenes **6** can serve as 3-hydroxypropanoyl anion equivalents (**B**).



The procedure we have developed for the synthesis of 3-benzyloxy-1-isocyanopropenes **6** is outlined in Scheme 1. Benzyloxy acetals **1**[3] were first converted into the corresponding methoxy nitriles **2** by reaction with cyanotrimethylsilane in the presence of boron trifluoride diethyl etherate. Reduction of these nitriles with lithiumaluminum hydride (LAH) gave the corresponding amines **3**, conversion of which into formamides **4** was effected in refluxing ethyl formate. Subsequent dehydration of **4** with phosphorous oxychloride and triethylamine gave the corresponding isocyanides **5**. Finally, treatment of **5** with lithium diisopropylamide (LDA) in tetrahydrofuran gave **6**. In Table 1 are listed the yields of the products. Compounds **6a** and **b** were both isolated as pale yellow liquid compounds by distillation and characterized by IR and ^{1}H NMR spectroscopies.[6] Both compounds are rather unstable, but storable at freezer temperature under argon for a few days.

The vinyl isocyanide **6a** could be lithiated with LDA in THF at -78 °C and the lithium reagent was treated



Reagents and conditions: i, Me_3SiCN, $BF_3(OEt_2)$, CH_2Cl_2, 0 °C; ii, $LiAlH_4$, Et_2O, 0 °C to r. t.; iii, HCO_2Et, reflux; iv, $POCl_3$, Et_3N, THF, 0 °C; v, LDA, THF, -78 °C.

Scheme 1.

Table 1. Preparation of 3-benzyloxy-1-isocyanopropenes **6**

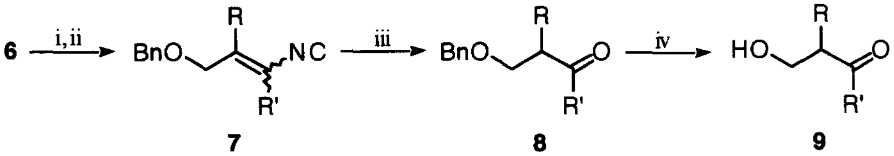
Entry	R	**2** (%)^a	**3** (%)^a	**4** (%)^a	**5** (%)^a	**6** (%)^a
a	H	90	95	90	81	81^b
b	Me	92	89	86	83	88^b

^{a}Isolated yields. ^{b}Ratio of *Z*/*E*= ca. 1:1

with alkyl halides. The alkylation reactions proceeded cleanly and were complete within 1 h at the same temperature, and gave the α-alkylation products **7a-d** in good yields. The lithiation and following alkylation with methyl iodide were found to be unaffected when the 2-hydrogen of **6a** was replaced by a methyl substituent, and the desired alkylated product **7e** could be obtained in a good yield. Table 2 includes results of the alkylation experiments. Products via the allylic metallation were not detected in these experiments. It is interesting to note that lithiation of **6** occurs exclusively at the α-position, not at the allylic position.[7]

A typical experimental procedure is given for the preparation of **7a**. To a stirred solution of LDA (1.0 mmol) in THF (10 ml) at -78 °C was added dropwise **6a** (0.17 g, 1.0 mmol). After 10 min iodomethane (0.16 g, 1.1 mmol) was added. The mixture was stirred for 1 h, and then quenched with saturated NH_4Cl solution and extracted with Et_2O. The extract was washed with brine, dried over anhyd $MgSO_4$, and evaporated. Purification of the residue by distillation using Kugelrohr afforded **7a** (0.18 g, 96%).[8]

Hydrolysis of compounds **7a-e** with concentrated HCl in THF at 0 °C for 10 min afforded the corresponding β-benzyloxyethyl ketones **8a-e** in high yields.[9] Hydrogenolysis of **8a-e** with 10% Pd on activated carbon under an atmosphere of hydrogen in ethyl acetate at room temperature led to the corresponding β-hydroxyethyl ketones **9a-e** in good yields.[10] These results are also listed in Table 2. This class of compounds is of interest as precursors for the generation of aldolate dianions[11a,b,12a] and as key intermediates in construction of a variety of important products,[12,13a] but their preparation by aldol-type processes can be difficult.[14] Although syntheses of **9a** and **e** by the reactions of formaldehyde with appropriate ketones have been reported previously, it is difficult to realize good yields under the normal liquid-phase condensation conditions due to the general complicated side reactions: reaction with more than one molecule of formaldehyde, subsequent reactions of the initially formed product such as dehydration, cyclization and polymerization, and self-condensation of the starting ketones.[11c,15a,16b] Compounds **9b**[11] and **9c**[16] are known in the literature, but their preparation by aldol-type processes has not yet been reported. Compound **9d** is a new product, and it is unlikely that this compound can be prepared by simple aldol-type processes.



Reagents and conditions: i, LDA, THF, -78 °C; ii, R'X, -78 °C; iii, aq. HCl, THF, 0 °C; iv, H_2 (1 atm), cat. 10% Pd/C, AcOEt, r.t.

Scheme 2.

Table 2. Preparation of **7** and their conversion into **9**.

Entry	**6**	R'X	**7** (Yield/%)[a]	**8** (Yield/%)[a]	**9** (Yield/%)[a]
1	**6a**	MeI	**7a** (96)[b]	**8a**[d] (91)	**9a**[e] (71)
2	**6a**	EtBr	**7b** (77)[b]	**8b** (89)	**9b**[f] (66)
3	**6a**	*n*-BuBr	**7c** (70)[b]	**8c** (87)	**9c**[g] (67)
4	**6a**	BnBr	**7d** (83)[c]	**8d** (88)	**9d** (71)
5	**6b**	MeI	**7e** (78)[b]	**8e** (78)	**9e**[h] (90)

[a] Isolated yields. [b] *Z*/*E* = ca. 1:1. [c] *Z*/*E* = ca. 7:3. [d] Ref. 13. [e] Identified by a direct comparison with a sample obtained commercially. [f] Ref. 11. [g] Ref. 16. [h] Ref. 15.

The results reported above demonstrate that 3-benzyloxy-1-isocyanopropenes can be used for the generation of 3-hydroxypropanoyl anion equivalents, and that the present process provides an efficient method for the preparation of β-hydroxyethyl ketones. Work on further synthetic applications utilizing reactions of these isocyanides with other electrophiles is now in progress and will be reported in due course.

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6. **6a**: Bp 113-115 °C/0.8 Torr; IR (neat) 2126, 1648, 1119 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.05 (1H, dd, *J*=4.2, 1.3 Hz), 4.29 (1H, d, *J*=4.4 Hz), 4.53 (2H, s), 5.6-6.4 (2H, m), 7.33 (5H, s); MS,

m/*z* (%) 173 (M$^+$, 1.6), 172 (12), 91 (100). HR MS Found: *m*/*z* 173.0820. Calcd for $C_{11}H_{11}NO$: M, 173.0840. **6b**: Bp 220 °C (bath temp)/2.0 Torr; IR (neat) 2122, 1102 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.75-1.9 (3H, m), 3.86 (1H, s), 4.26 (1H, s), 4.43 (2H, s), 5.45-6.6 (0.5H, m), 5.7-5.85 (0.5H, m), 7.26 (5H, s); MS, *m*/*z* (%) 187 (M$^+$, 2.1), 186 (19), 91 (100). HR MS Found: *m*/*z* 187.0995. Calcd for $C_{12}H_{13}NO$: M, 187.0997.

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8. Selected physical and spectral data of **7** are as follows. **7a**: Bp 107-110 °C (bath temp)/0.35 Torr; IR (neat) 2110, 1665, 1070 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.92 and 1.98 (combined 3H, 2br. s), 4.03 (1H, d, J=6.8 Hz), 4.21 (1H, d, J=5.3 Hz), 4.50 and 4.52 (2H, 2s), 5.45-6.05 (1H, m), 7.33 (5H, s); MS, *m*/*z* (%) 187 (M$^+$, 1.5), 186 (5.5), 118 (16), 96 (18), 91 (100). HR MS Found: *m*/*z* 187.0984. Calcd for $C_{12}H_{13}NO$: M, 187.0997. **7e**: Bp 170 °C (bath temp)/1.4 Torr; IR (neat) 2108, 1661, 1073 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.74 (1.5H, s), 1.90 (4.5H, s), 3.89 (1H, s), 4.12 (1H, s), 4.41 (2H, s), 7.17 (5H, s); MS, *m*/*z* (%) 201 (M$^+$, 1.9), 200 (3.6), 91 (100). HR MS. Found: *m*/*z* 201.1160. Calcd for $C_{13}H_{15}NO$: M, 201.1154.
9. Selected physical and spectral data of **8** are as follows. **8b**: R_f 0.44 (1:3, EtOAc-hexane); IR (neat) 1714, 1105 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.05 (3H, t, J=7.2 Hz), 2.46 (2H, q, J=7.2 Hz), 2.69 (2H, t, J=6.4 Hz), 3.74 (2H, t, J=6.4 Hz), 4.50 (2H, s), 7.31 (5H, s); MS, *m*/*z* (%) 193 (0.98), 192 (M$^+$, 0.37), 120 (13), 91 (100). HR MS. Found:*m*/*z* 192.1139. Calcd for $C_{12}H_{16}O_2$: M, 192.1139. **8c**: Bp 104-107 °C (bath temp)/0.35 Torr; IR (neat) 1715, 1103 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (3H, t, J=6.5 Hz), 1.1-1.7 (4H, m), 2.44 (2H, t, J=7.3 Hz), 2.69 (2H, t, J=6.4 Hz), 3.74 (2H, t, J=6.4 Hz), 4.50 (2H, s), 7.31 (5H, s); MS, *m*/*z* (%) 220 (M$^+$, 2.8), 219 (16), 192 (27), 105 (100). HR MS. Found: *m*/*z* 220.1439. Calcd for $C_{14}H_{20}O_2$: M, 220.1464.
10. **9d**: R_f 0.41 (1:1, EtOAc-hexane); IR (neat) 3360, 1710, 1051 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.2-2.5 (1H, br), 2.69 (2H, t, J=5.5 Hz), 3.6-3.9 (4H, m), 7.1-7.4 (5H, m); MS, *m*/*z* (%) 164 (M$^+$, 16), 91 (66), 73 (100). HR MS. Found: *m*/*z* 164.0822. Calcd for $C_{10}H_{12}O_2$: M, 164.0838.
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