Facile Homologation of N,N-Dialkyl-α-bromoacetamide by Trialkylboranes in the Presence of Lithium Diisopropylamide

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The homologation reactions of α-halocarbonyl and α-halosulfonyl compounds with organoboranes represent a highly efficient way to increase the length of the carbon skeletons of olefins by one, two, or more carbon atoms, with the simultaneous introduction of functional groups.[1] For example, organoboranes react with α-halo esters,[2] α-halo ketones,[3] α-halo nitrile,[4] and α-halosulfonyl compounds[5] to give the corresponding higher esters, ketones, nitriles, and sulfonyl compounds, in the presence of a steric base such as potassium *tert*-butoxide or potassium 2,6-di-*tert*-butylphenoxide. Although the homologation of *N,N*-dialkyl-α-bromoacetamide can be accomplished indirectly by the reaction of trialkylborane with *N,N*-dialkyl-(dimethylsulfuranylidene)acetamide (prepared from *N,N*-dialkyl-α-bromoacetamide, dimethyl sulfide, and NaH),[6] no method for the direct homologation of *N,N*-dialkyl-α-bromoacetamide by organoborane has appeared in literature.

Recently, we found that trialkylborane could not react with *N,N*-dialkyl-α-bromoacetamide in the presence of potassium *tert*-butoxide or potassium 2,6-di-*tert*-butyl-4-methylphenoxide. We also found that EtONa–EtOH could induce the reaction of (carbethoxymethyl)dimethylsulfonium bromide (which was generated from ethyl α-bromoacetate and dimethyl sulfide) with trialkylborane to result in the indirect homologation of ethyl α-bromoacetate. However, (((diethylamino)carbonyl)methyl)-dimethylsulfonium bromide, generated from *N,N*-diethyl-α-bromoacetamide and dimethyl sulfide, did not react with trialkylborane under the same conditions.[7] This result suggests that α-sulfonium-substituted *N,N*-diethylamides are more difficult to deprotonate than α-sulfonium-substituted esters. In addition, the acidity of the α-position of *N,N*-dialkyl-α-bromoacetamide is weaker than that of an α-sulfonium-substituted *N,N*-dialkylamide. Thus, potassium *tert*-butoxide or potassium 2,6-di-*tert*-butyl-4-methylphenoate (which is similar to EtONa) might deprotonate *N,N*-dialkyl-α-bromoacetamide only with difficulty. This may be why the reaction of *N,N*-dialkyl-α-bromoacetamide with trialkylborane could not be induced by potassium alkoxide.

Since lithium diisopropylamide is a non-nucleophilic strong base, we employed it to induce the reaction of *N,N*-dialkyl-α-bromoacetamide with trialkylboranes. Herein, we report our results of the direct homologation of *N,N*-dialkyl-α-bromoacetamide by trialkylborane in the presence of lithium diisopropylamide.

The procedure is very facile. Trialkylboranes, which are easily prepared by the hydroboration of olefins with diborane in THF, readily react with *N,N*-dialkyl-α-bromoacetamide under the influence of lithium diisopropylamide to afford alkylated *N,N*-dialkylacetamides in 48–94% GC yields (isolated yields are 41–80%) as shown in Scheme I.

The reactions of various trialkylboranes with several *N,N*-dialkyl-α-bromoacetamides were studied, and the results are shown in Table I.

The reaction affords alkylated *N,N*-dialkylacetamides in good yields. Thus, the present procedure provides an efficient and direct route to higher amides from *N,N*-dialkyl-α-bromoacetamide and olefins. Unfortunately, our attempts to induce the reaction of *N*-propyl-α-bromoacetamide or α-iodoacetamide with trialkylborane by lithium diisopropylamide were unsuccessful. It might be that the nitrogen atom is more easily deprotonated than the α-carbon of these α-haloamides.[8] Table I shows that in the case of R^2 = i-Pr (entries 7 and 8), the yields of the corresponding amides are low, presumably due to the steric bulkiness of the (diisopropylamino)carbonyl group, which hinders the attack of the α-halocarbon anion intermediate on trialkylborane. The mechanism may be depicted as in Scheme II.

The reaction of 9-hexyl-9-BBN with *N,N*-diethyl-α-bromoacetamide in the presence of LDA was also investigated, and the results are shown in Scheme III.

Scheme III shows that after 8 h at room temperature the yield of *N,N*-diethyloctanamide reached 58%. Although this is a modest yield, the decreased alkene requirement when using 9-BBN as the hydroboration agent might be compensation in the case of expensive alkenes.

The reaction of *N,N*-dimethyl-α-bromoacetamide with trialkylboranes also afforded the corresponding homologated amides in good yield, but in the case of secondary organoborane or *N,N*-dialkyl-α-bromopropanamide, the yields of the corresponding α-alkylated amides are decreased.

We are continuing to extend the scope of this method and will report further results accordingly.

The preparation of *N,N*-diethyloctanamide (**3a**) is representative: To the solution of hexene–1 (0.63 g, 7.5 mmol) in THF (10 mL) under nitrogen was slowly added drop-by-drop the solution of borane (1.17 mL, 2.14 M, 2.5 mmol) at 0 °C. The reaction was stirred at room temperature for 30 min. To the solution of trihexylborane in THF were sequentially added *N,N*-diethyl-α-bromoacetamide (0.49 g, 2.5 mmol) and the solution of LDA (2.5 mmol) in THF (5 mL) at −78 °C. After the reaction was carried out at −78 °C for 30 min, the reaction was continued at rt for 3 h. GC analysis of the reaction mixture, followed by addition of *n*-tridecane as internal standard, indicated

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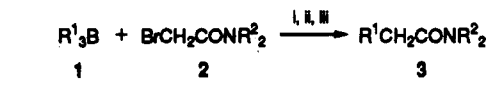
Scheme I[a]



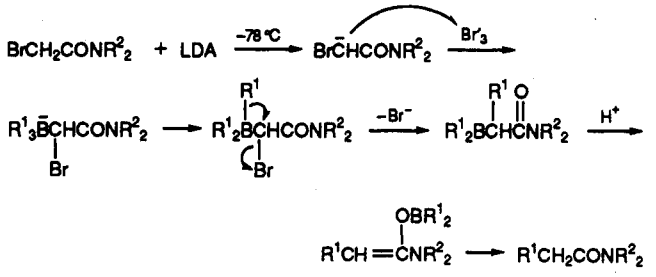
[a] Key: (i) LDA, −78 °C → rt, 30 min; (ii) rt, 2–5 h; (iii) H_2O_2/OAc⁻.

Table I. Reaction of Trialkylboranes (R^1_3) with *N,N*-Dialkyl-α-bromoacetamides ($BrCH_2CONR^2_2$)

entry	R^1	R^2	*t* (h)	product[a]	yield[b] (%)
1	*n*-C_6H_{13}	Et	3	*n*-$C_7H_{15}CONEt_2$ (**3a**)	94 (80)
2	*n*-C_7H_{15}	Et	2	*n*-$C_8H_{17}CONEt_2$ (**3b**)	(71)
3	*n*-C_8H_{17}	Et	2	*n*-$C_9H_{19}CONEt_2$ (**3c**)	(70)
4	*n*-C_6H_{13}	*n*-Bu	3	*n*-$C_7H_{15}CON(Bu\text{-}n)_2$ (**3d**)	91 (78)
5	*n*-C_7H_{15}	*n*-Bu	5	*n*-$C_8H_{17}CON(Bu\text{-}n)_2$ (**3e**)	85 (71)
6	*n*-C_8H_{17}	*n*-Bu	5	*n*-$C_9H_{19}CON(Bu\text{-}n)_2$ (**3f**)	80 (70)
7	*n*-C_6H_{13}	*i*-Pr	4	*n*-$C_7H_{15}CON(i\text{-}pr)_2$ (**3g**)	48 (40)
8	*n*-C_8H_{17}	*i*-Pr	4	*n*-$C_9H_{19}CON(i\text{-}Pr)_2$ (**3h**)	(41)

[a] All structures were confirmed by ^1H NMR, IR, MS, HRMS, n_D, or bp. [b] Yields were determined by GC; the values in parentheses are the isolated yields.

Scheme II



Scheme III[a]

entry	*t* (h)	yield[b] (%)
1	2	48
2	4	52
3	6	57
4	8	58

[a] Key: (i) LDA, −78 °C → rt, 1 h; (ii) rt, 2–8 h; (iii) H_2O_2/OAc⁻.[b] The yields were determined by GC.

a 94% yield of *N,N*-diethyloctanamide. The reaction mixture was oxidized by H_2O_2 (2 mL, 30%) and NaOAc (2 mL, 3 N) at 0 °C for 1 h and then extracted with ethyl ether, dried by $MgSO_4$, and isolated by silica column chromatography to give 0.40 g (80% yield) of *N,N*-diethyloctanamide (**3a**): n^{25}_D = 1.4486, (lit.[9] n^{25}_D = 1.4482.

Experimental Section

3a. n^{25}_D = 1.4486 (lit.[9] n^{25}_D = 1.4482). MS (EI) *m/z*: 200 (M + 1, 60.07), 198 (M − 1, 4.18), 184 (3.16), 170 (5.97), 156 (3.43), 142 (10.03), 128 (44.22), 115 (80.59), 100 (63.02), 72 (48.15), 58 (100.00), 57 (44.45), 44 (47.07), 43 (37.44). IR (film) ν_{max}: 1650 (s), 1380 (s), 1365 (s) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.60–1.60 (m, 19H, 3 CH_3, 5 CH_2), 2.08 (t, 2H, *J* = 7 Hz, $CH_2C{=}O$), 3.20 (q, 4H, *J* = 7 Hz, $CON(CH_2{-})_2$) ppm.

3b. n^{25}_D = 1.4485 (lit.[9] n^{25}_D = 1.4493). MS (EI) *m/z*: 214 (M + 1, 66.07), 213 (M, 4.23), 113 (8.27), 99 (10.10), 85 (30.80), 71 (100.00). IR (film) ν_{max}: 1645 (s), 1380 (s), 1365 (m) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.60–1.60 (m, 21H), 2.10 (t, 2H, *J* = 7 Hz), 3.19 (q, 4H, *J* = 7 Hz) ppm.

3c. n^{25}_D = 1.4498 (lit.[9] n^{25}_D = 1.4505). MS (EI) *m/z*: 228 (M + 1, 9.51), 227 (M, 2.56), 128 (20.25), 115 (43.21), 100 (22.04), 85 (21.95), 71 (93.33), 57 (100.00), 43 (97.97). IR (film) ν_{max}: 1645 (s), 1380 (s), 1365 (m) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.60–1.60 (m, 23H), 2.11 (t, 2H, *J* = 7 Hz), 3.20 (q, 4H, *J* = 7 Hz) ppm.

3d. HRMS for $C_{16}H_{33}NO$: calcd, M = 255.2562; found, M = 255.2531. MS (EI) *m/z*: 256 (M + 1, 100.00), 254 (M − 1, 15.32), 198 (2.49), 184 (6.32), 171 (3.03), 156 (19.85), 128 (29.39), 100 (9.41), 86 (58.39), 72 (3.35), 57 (30.38), 44 (17.93), 43 (8.80). IR (film) ν_{max}: 1645 (s), 1380 (s) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.88 (m, 9H, 3 CH_3), 1.24 (br s, 18H, 9 CH_2), 2.11 (t, 2H, *J* = 6.5 Hz, $CH_2C{=}O$), 3.15 (t, 4H, *J* = 7 Hz, $CON(CH_2{-})_2$) ppm.

3e. Bp: 143–145 °C/1 mmHg (lit.[10] bp 170–175 °C/4 mmHg). MS (EI) *m/z*: 270 (M + 1, 44.52), 254 (1.65), 240 (2.72), 226 (4.43), 212 (2.35), 198 (5.00), 184 (18.22), 156 (25.57), 141 (12.95), 128 (48.73), 114 (18.08), 100 (22.83), 86 (100.00), 71 (23.83), 57 (66.11), 43 (70.72). IR (film) ν_{max}: 1645 (s), 1380 (s) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.90 (m, 9H), 1.25 (br s, 20H), 2.12 (t, 2H, *J* = 6.5 Hz), 3.17 (t, 4H, *J* = 7 Hz) ppm.

3f. Bp: 155–156 °C/1 mmHg (lit.[10] bp 155–157 °C/1 mmHg). MS (EI) *m/z*: 284 (M + 1, 100.00), 282 (M − 1, 6.25), 157 (12.39), 128 (27.21), 100 (9.75), 86 (58.22), 71 (5.82), 57 (23.95), 43 (35.23). IR (film) ν_{max}: 1645 (s), 1380 (s) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.89 (m, 9H), 1.22 (br s, 22H), 2.12 (t, 2H, *J* = 6.5 Hz), 3.17 (t, 4H, *J* = 7 Hz) ppm.

3g. HRMS for $C_{14}H_{29}NO$: calcd, M = 227.2249; found, M = 227.2271. MS (EI) *m/z*: 229 (M + 2, 100.00), 228 (M + 1, 89.09), 227 (M, 0.40), 226 (M − 1, 17.59), 212 (7.96), 184 (21.38), 100 (19.77), 86 (93.99), 70 (6.61), 58 (26.25), 43 (20.82). IR (film) ν_{max}: 1645 (s), 1375 (s), 1340 (m) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.89 (t, 3H, *J* = 5 Hz, CH_3), 1.05–1.85 (m, 22H, 5 CH_2, 2 $C(CH_3)_2$), 2.17 (t, 2H, *J* = 6.5 Hz, $CH_2C{=}O$), 3.10–4.27 (m, 2H, $CON(CH{-})_2$) ppm.

3h. HRMS for $C_{16}H_{33}NO$: calcd, M = 255.2562; found, M = 255.2564. MS (EI) *m/z*: 256 (M + 1, 94.77), 254 (M − 1, 5.45), 212 (19.34), 100 (29.33), 86 (100.00), 71 (6.32), 58 (36.70), 43 (37.51). IR (film) ν_{max}: 1645 (s), 1375 (s), 1340 (m) cm⁻¹. ^1H NMR (CCl_4/TMS, 60 MHz) δ: 0.88 (t, 3H, *J* = 5 Hz), 1.00–1.85 (m, 26H), 2.18 (t, 2H, *J* = 6.5 Hz), 3.10–4.26 (m, 2H) ppm.

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