

## New Method for the Selective Reduction of Amides

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A new procedure was developed for the reduction of tertiary aliphatic, olefinic, and aromatic amides to aldehydes. Reaction of the amides (1), (5), (7), (9), (11), (13), (15), and (17) with ethyl or methyl trifluoromethanesulphonate in  $\text{CH}_2\text{Cl}_2$  at room temperature and then with L-Selectride at  $-78^\circ\text{C}$  gave the corresponding aldehydes (2), (6), (8), (10), (12), (14), (16), and (18), respectively. A second functional group, including  $\text{CO}_2\text{R}$ ,  $\text{C}=\text{C}$ ,  $\text{CH}(\text{OCH}_2\text{CH}_2\text{O})$ , and  $\text{C}\equiv\text{N}$ , in these amides was found to be inert under the conditions employed. These selective reductions gave the desired aldehydes in 50–73% isolated yields and in >95% yields based on converted amides.

Amides can be converted into aldehydes in satisfactory yields by several reducing agents, such as  $\text{LiAlH}_4$ ,<sup>1–3</sup>  $\text{LiAlH}(\text{OEt})_3$ ,<sup>4,5</sup> and  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2$ .<sup>6</sup> Only a few procedures however can lead to aldehydes efficiently by reduction of amides that contain other readily reducible functional groups.<sup>7</sup> We now report a solution to this problem by use of alkyl trifluoromethanesulphonates and L-Selectride.

### Results

We treated amido ester (1) with ethyl trifluoromethanesulphonate<sup>8</sup> (EtOTf; 1.05 equiv.) in  $\text{CH}_2\text{Cl}_2$  at room temperature for 24 h. After the solvent was removed completely, the residue was dissolved in THF and treated with a reducing agent (2.0 equiv.) at low temperature. Among the various reducing agents tested, we found that Super-Hydride,<sup>9,10</sup> L-Selectride,<sup>11,12</sup> LS-Selectride,<sup>13</sup> K-Selectride,<sup>14,15</sup> and  $\text{LiAlH}(\text{OBu})_3$ <sup>16–18</sup> gave the most satisfactory results (see Table 1). Analysis by GC indicated that the reaction products contained up to three components: the desired aldehyde (2), the by-product diester (3) if any, and recovered starting material (1). When replacing EtOTf with methyl trifluoromethanesulphonate<sup>8</sup> (MeOTf), we obtained similar results except that the by-product diester (4), instead of the diester (3), was formed.

Use of the conditions listed in entry 3 of Table 1, involving EtOTf and L-Selectride at  $-87^\circ\text{C}$ , provided the best results for the formation of the desired product (2). The reductions at  $-78^\circ\text{C}$  and  $-87^\circ\text{C}$  (entries 2 and 3) gave a comparable ratio of (2):(1). Reduction proceeded faster at  $-78^\circ\text{C}$  than at  $-87^\circ\text{C}$ . Also, control of temperature at  $-78^\circ\text{C}$  can be easily accomplished by use of a solid  $\text{CO}_2$ -acetone cooling bath. Consequently we adopted the conditions listed in entry 2 of Table 1 for the reduction of various amides.

By using EtOTf and L-Selectride at  $-78^\circ\text{C}$ , we converted the amides (1), (5), (7), (9), (11), (13), (15), and (17) into the corresponding aldehydes (2), (6), (8), (10), (12), (14), (16), and (18), respectively (Table 2). The isolated yields of these aldehydes were in the range 50–73%. Analyses by GC and TLC showed that the crude products from these reactions contained only two components: the desired aldehyde and recovered starting material. Thus the yields of these reactions were better than 95% based on the converted amides.

### Discussion

The Scheme shows a plausible pathway that can illustrate the results summarized in Table 1. Initially EtOTf activates the amido group in (1) to give the intermediate (19).<sup>19</sup> This step is

**Table 1.** Product distributions [(2):(3):(1) and (2):(4):(1)] determined by GC for the reaction of the amido ester (1) with 1.05 equiv. of alkyl triflate in  $\text{CH}_2\text{Cl}_2$  at room temperature for 24 h and then with various reducing agents in THF at  $-78^\circ\text{C}$ , except otherwise stated. All of the conversions provided >98% yields based on the mass balance.

Entry	Triflate	Reducing agent (equiv.) <sup>a</sup>	Time (h)	(2) : (3) : (1)
1	EtOTf	Super-Hydride (2.0)	1.5	0.68:0.12:1.0
2	EtOTf	L-Selectride (2.0)	1.5	2.22:0 :1.0
3	EtOTf	L-Selectride (2.0) <sup>b</sup>	3.5	2.51:0 :1.0
4	EtOTf	LS-Selectride (2.0)	1.5	2.10:0.64:1.0
5	EtOTf	K-Selectride (2.0)	1.5	1.32:0 :1.0
6	EtOTf	$\text{LiAlH}(\text{OBu})_3$ (2.0)	1.5	2.00:0.58:1.0
7	EtOTf	$\text{LiAlH}(\text{OBu})_3$ (2.0)	4.0	1.40:0.56:1.0
				(2) : (4) : (1)
8	MeOTf	L-Selectride (1.05)	1.0	1.53:0.55:1.0
9	MeOTf	L-Selectride (2.0)	1.0	1.66:0 :1.0

<sup>a</sup> Super-Hydride =  $\text{LiBHEt}_3$ , L-Selectride =  $\text{LiBH}(\text{CHMeEt})_3$ , LS-Selectride =  $\text{LiBH}(\text{CHMeCHMe}_2)_3$ , and K-Selectride =  $\text{KBH}(\text{CHMeEt})_3$ . <sup>b</sup> The reduction step involving L-Selectride was carried out at  $-87^\circ\text{C}$ .

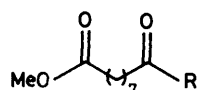
**Table 2.** Reduction of amides to aldehydes by use of 1.05 equiv. of EtOTf in  $\text{CH}_2\text{Cl}_2$  at room temperature and 2.0 equiv. of L-Selectride in THF at  $-78^\circ\text{C}$ , except otherwise stated.

Amide	Aldehyde	Isolated yield of aldehyde (%)	Yield of recovered starting material (%)
(1)	(2)	69	30
(5)	(6)	62	35
(7)	(8)	73	25
(9)	(10)	67	32
(11)	(12)	56	42
(13)	(14)	52	46
(15)	(16)	67	31
(17) <sup>a</sup>	(18)	50	—

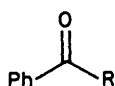
<sup>a</sup> Reaction of MeOTf (5.0 equiv.) with (17) was carried out at room temperature for 4 days before L-Selectride (1.1 equiv.) was added.

similar to Borch's strategy<sup>20</sup> in his two-step reduction of amides to amines with  $\text{NaBH}_4$ . He utilized  $\text{Et}_3\text{OBF}_4$  to activate amides. We found that the alkylating agent EtOTf worked

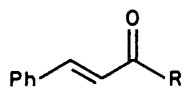
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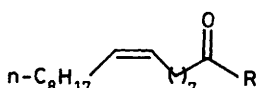
- (1) R = NMe<sub>2</sub>  
 (2) R = H  
 (3) R = OEt  
 (4) R = OMe



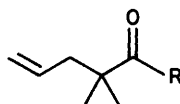
- (5) R = NMe<sub>2</sub>  
 (6) R = H



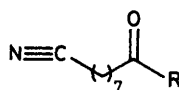
- (7) R = NMe<sub>2</sub>  
 (8) R = H



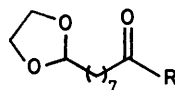
- (9) R = NMe<sub>2</sub>  
 (10) R = H



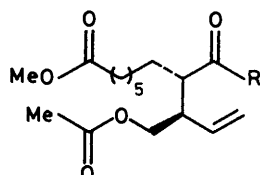
- (11) R = NMe<sub>2</sub>  
 (12) R = H



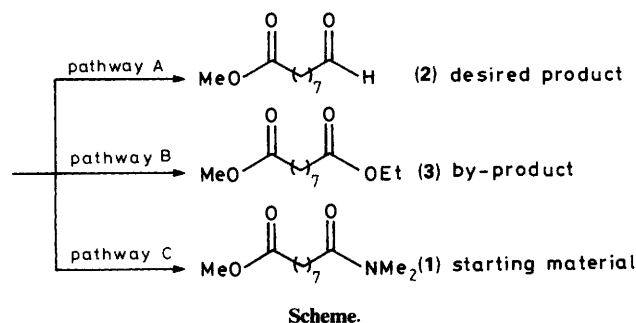
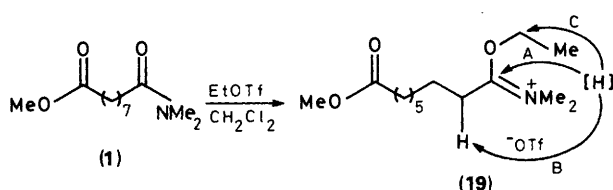
- (13) R = NMe<sub>2</sub>  
 (14) R = H



- (15) R = NMe<sub>2</sub>  
 (16) R = H



- (17) R = NMe<sub>2</sub>  
 (18) R = H



better for bifunctional amides (1), (5), (7), (9), (11), (13), and (15). The amido group in (17) locates in a sterically hindered area. Thus an excess of the less bulky reagent MeOTf was used and the alkylation required 4 days (Table 2).

Metal hydride reducing agents may react with the intermediate (19) at one of three centres. Bredereck *et al.* reported a related example of the reaction between RC(OEt)=N<sup>+</sup>R'<sub>2</sub> and EtO<sup>-</sup>.<sup>21</sup> Attack at the C=N<sup>+</sup> carbon of (19) by a reducing agent (pathway A) would lead to the desired aldehyde (2).

Bulkier reagents, such as LS-Selectride and LiAlH(OBu<sup>t</sup>)<sub>3</sub>, have a greater potential to attack the α-hydrogen, a centre with

least steric hindrance. This pathway (*i.e.* pathway B) could lead to the ester (3) via a ketene O,N-acetal.

Reducing agents may also react with (19) at the hindered methylene carbon to give (1), as shown by pathway C. The ratios of (2):(3):(1) in Table 1 show that this process occurred to a significant extent when we used the less bulky reagent Super-Hydride.

We conclude that metal hydrides with larger ligands make pathway B more competitive and with smaller ligands favour pathway C. L-Selectride possesses medium-sized ligands and served as the best reducing agent for (19).

For the reduction of amides to aldehydes, L-Selectride in combination with EtOTf supplements other well recognized reagents, including 3-methylbutan-2-ylborane<sup>7</sup> and lithium triethoxyaluminumhydride.<sup>4</sup> Brown *et al.* reported that 3-methylbutan-2-ylborane also can react slowly with nitriles [*cf.* (13) → (14)] and hydroborate C=C double bonds [*cf.* (9) → (10), (11) → (12), and (17) → (18)]. Lithium triethoxyaluminumhydride attacks α,β-unsaturated amides at the C=C double bond preferentially<sup>4</sup> [*cf.* (7) → (8)].

### Experimental

Reduction of the amide (1) to the aldehyde (2) represents a general procedure. For individual substrates, the reaction conditions are listed in Table 2.

A solution of the amide (1) (193 mg, 0.842 mmol, 1.0 equiv.) and EtOTf (116 μl; 0.884 mmol, 1.05 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 ml) was stirred at room temperature for 24 h. The solvent was removed by rotary evaporation at 35 °C and the residue, a pale purple oil, was placed under high vacuum until it reached constant weight. L-Selectride (1.0M in THF, 1.68 ml; 1.68 mmol, 2.0 equiv.) was then added over 3 min to the solution containing the pale purple oil and THF (2.5 ml) at -78 °C. The colour of the solution changed to pale yellow during the addition. After 1.5 h at -78 °C, the mixture was immersed in an ice-bath and then treated with saturated aqueous NH<sub>4</sub>Cl (2.0 ml). The mixture was diluted with a small amount of water and extracted three times with Et<sub>2</sub>O. The combined ethereal layers were washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>), and filtered. Solvents were removed and the resulting pale yellow liquid was chromatographed by use of a Chromatotron (1-mm plate, 10% EtOAc in hexanes as eluant) to give the pure aldehyde (2) (69%, 107 mg, 0.573 mmol): TLC *R<sub>F</sub>* 0.36 (20% EtOAc in hexanes); δ(CDCl<sub>3</sub>, 80 MHz) 1.20–1.83 (m, 10 H, 5 × CH<sub>2</sub>), 2.21–2.50 (m, 4 H, 2 × CH<sub>2</sub>CO), 3.66 (s, 3 H, OCH<sub>3</sub>), and 9.76 (t, *J* 1.8 Hz, 1 H, CHO); ν<sub>max</sub>(neat) 2940s, 2862m, 1734s (C=O), 1442m, 1205m, (C–O), and 1176m cm<sup>-1</sup> (C–O). Its physical properties and spectroscopic characteristics are consistent with those reported in the literature.<sup>22</sup>

The spectroscopic data of other reduction products are listed as follows. For (6): TLC *R<sub>F</sub>* 0.40 (5% EtOAc in hexanes); δ(CDCl<sub>3</sub>) 7.29–7.60, 7.65–8.12 (m, 5 H, C<sub>6</sub>H<sub>5</sub>), and 10.02 (s, 1 H, CHO); ν<sub>max</sub>(neat) 3135s (=CH), 2798s, 2715m (O=CH), 1685s (C=O), 1591m (C=C), 1580m, 1450w, 1309w, 1284m, 1199s, 936w, 715m, and 690m cm<sup>-1</sup>.

For (8): TLC *R<sub>F</sub>* 0.42 (10% EtOAc in hexanes); δ(CDCl<sub>3</sub>) 6.60 (d, *J* 7.5 Hz, 1 H, =CH), 6.80 (d, *J* 7.5 Hz, 1 H, =CH), 7.38–7.60 (m, 5 H, C<sub>6</sub>H<sub>5</sub>), and 9.71 (d, *J* 7.6 Hz, 1 H, CHO); ν<sub>max</sub>(neat) 3155m, 3124m (=CH), 2804m, 2736m (O=CH), 1667s (C=O), 1628s (C=C), 1579m, 1454s, 1299m, 1254w, 1127s, 979s 756s, and 697s cm<sup>-1</sup>.

For (10): TLC *R<sub>F</sub>* 0.33 (5% EtOAc in hexanes); δ(CDCl<sub>3</sub>) 0.78–1.01 (m, 3 H, CH<sub>3</sub>), 1.15–1.45, 1.56–1.70 (m, 22 H, 11 × CH<sub>2</sub>), 1.86–2.14 (m, 4 H, 2 × C=CCH<sub>2</sub>), 2.40 (t, *J* 7.0 Hz, 2 H, CH<sub>2</sub>CO), 5.34 (t, *J* 4.6 Hz, 2 H, CH=CH), and 9.76 (t, *J* 1.9 Hz, 1 H, CHO); ν<sub>max</sub>(neat) 3000m, 2923s, 2852s (O=CH), 1691s (C=O), 1456s, 1380w, 1140m, and 964m cm<sup>-1</sup>.

For (12): TLC *R<sub>F</sub>* 0.34 (10% EtOAc in hexanes); δ(CDCl<sub>3</sub>)

1.05 (s, 6 H, 2 × CH<sub>3</sub>), 2.22 (d, *J* 7.2 Hz, 2 H, CH<sub>2</sub>), 5.15 (d, *J* 1.2 Hz, 2 H, =CH<sub>2</sub>), 5.56 (t, *J* 7.2 Hz, 1 H, =CH), and 9.48 (s, 1 H, CHO);  $\nu_{\max}(\text{neat})$  3 072w (=C-H), 2 960s, 2 919m, 2 872m, 2 802w, 2 696m (O=CH), 1 725s (C=O), 1 637m (C=C), 1 467m, 1 390w, 1 367w, 1 190w, 1 155w, 991m, 914m, 867m, and 767w cm<sup>-1</sup>. Its physical properties and spectroscopic characteristics are consistent with those reported in the literature.<sup>23</sup>

For (14): TLC *R<sub>F</sub>* 0.25 (30% EtOAc in hexanes);  $\delta(\text{CDCl}_3)$  1.17–1.80 (m, 10 H, 5 × CH<sub>2</sub>), 2.25–2.44 (t, *J* 7.4 Hz, 4 H, CH<sub>2</sub>CO + CH<sub>2</sub>CN), and 9.76 (t, *J* 1.7 Hz, 1 H, CHO);  $\nu_{\max}(\text{neat})$  2 924s, 2 858s, 2 720m (O=CH), 2 242m (CN), 1 718s (C=O), 1 460m, 1 420m, 1 371m, 890w, and 726w cm<sup>-1</sup> [Found: *m/z* 152.1079 (*M*<sup>+</sup> - H). Calc. for C<sub>9</sub>H<sub>15</sub>NO: 152.1075].

For (16): TLC *R<sub>F</sub>* 0.33 (20% EtOAc in hexanes);  $\delta(\text{CDCl}_3)$  1.24–1.82 (m, 12 H, 6 × CH<sub>2</sub>), 2.40 (t, *J* 7.1 Hz, 2 H, CH<sub>2</sub>CO), 3.78–3.99 (m, 4 H, 2 × CH<sub>2</sub>O), 4.83 (t, *J* 4.5 Hz, 1 H, CHO<sub>2</sub>), and 9.78 (t, *J* 1.8 Hz, 1 H, CHO);  $\nu_{\max}(\text{neat})$  2 923s, 2 853s, 2 713m (O=CH), 1 718s (C=O), 1 458w, 1 407m, 1 350w, 1 138s (C-O), 1 033s (C-O), and 948m cm<sup>-1</sup> [Found: *m/z* 200.1388 (*M*<sup>+</sup>). Calc. for C<sub>11</sub>H<sub>20</sub>O<sub>3</sub>: 200.1412].

For (18): TLC *R<sub>F</sub>* 0.57 (40% EtOAc in hexanes);  $\delta(\text{CDCl}_3)$  1.22–1.75 (m, 10 H, 5 × CH<sub>2</sub>), 2.04 (s, 3 H, CH<sub>3</sub>CO), 2.30 (t, *J* 7.4 Hz, 2 H, CH<sub>2</sub>CO<sub>2</sub>), 2.38 (m, 1 H, CHCO), 2.79 (m, 1 H, CHC=C), 3.67 (s, 3 H, OCH<sub>3</sub>), 4.10 (dd, *J* 7.2, 10.8 Hz, 1 H, CHOCO), 4.16 (dd, *J* 6.4, 10.8 Hz, 1 H, CHOCO), 5.12–5.22 (m, 2 H, =CH<sub>2</sub>), 5.73 (m, 1 H, C=CH), and 9.63 (d, *J* 2.4 Hz, 1 H, CHO);  $\nu_{\max}(\text{neat})$  3 083w (=C-H), 2 939s, 2 865s, 2 724m (O=C-H), 1 722s (C=O), 1 641m (C=C), 1 466m, 1 439m, 1 369m, 1 237s (C-O), 1 175s (C-O), 1 039m (C-O), 932m, and 736w cm<sup>-1</sup> [Found: *m/z* 297.1700 (*M*<sup>+</sup> - H). Calc. for C<sub>16</sub>H<sub>25</sub>O<sub>5</sub>: 297.1702].

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