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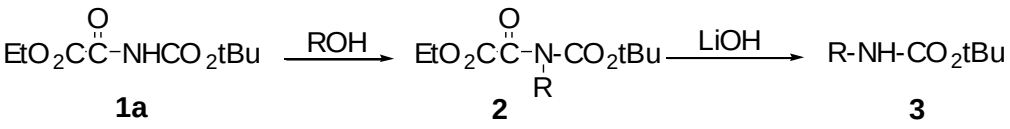
N-BOC AND N-CBZ ETHYL OXAMATES : NEW GABRIEL REAGENTS.

Fabienne Berrée,* Jean-Pierre Bazureau,
Gwendal Michelot and Maurice Le Corre

Laboratoire de Synthèse Organique, Associé au CNRS.
Avenue du Général Leclerc, 35042 Rennes, France.

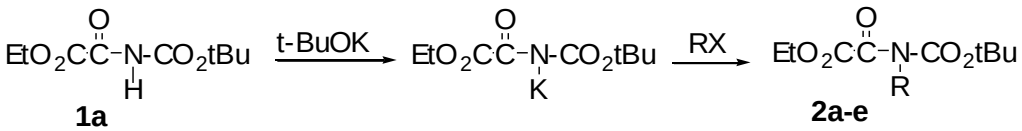
Abstract : N-Boc and N-CBz ethyl oxamates can be directly coupled with various halides under Gabriel conditions which afford the corresponding N-protected amines after mild deprotection with LiOH.

We recently reported the use of the N-Boc ethyl oxamate **1a** in Mitsunobu reactions.[1] The condensation products **2** could be easily deprotected in N-Boc amines **3** by using LiOH (Scheme 1).



Scheme 1

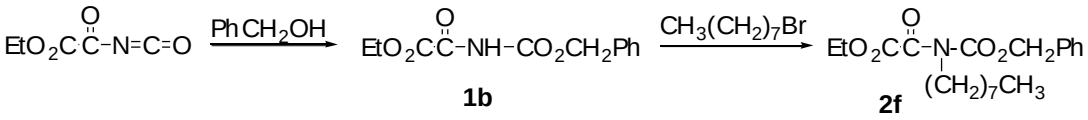
Despite of the high sensitivity of ethoxalyl group to weak nucleophiles, we observed that it was also possible to generate the potassium salt by treatment of **1a** with t-BuOK. Then this salt was used in Gabriel reactions[2,3] (Scheme 2).



Scheme 2

The reactions were carried out in DMF at 60°C during 1 hour and led to the N-alkylated ethyl oxamates **2** in good yields (Table 1). For the reaction with 1,4-dibromobutane, we have observed that two equivalents of the salt have reacted with one equivalent of 1,4-dibromobutane to give the bis-condensed product (entry e), but the use of an excess of bromide derivative allowed to obtain essentially the single condensation product **2e**.

We also extended this methodology to the preparation of the N-CBz ethyl oxamate **1b**. This product can be selectively deprotected by catalytic hydrogenation. It was prepared in quantitative yield by reaction of benzyl alcohol with ethyloxalyl isocyanate[4] in toluene under anhydrous conditions (Scheme 3). The compound **1b** showed a similar reactivity to **1a** when it was coupled with 1-bromooctane (entry f).



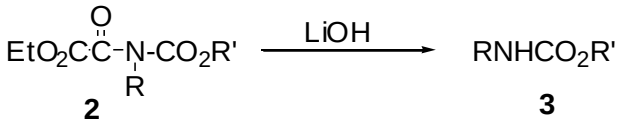
Scheme 3

Table 1. Conversion of bromide derivatives to oxamates **2**.

entry	**1**	**RX**	**2** Yield[a] (%)
a	**1a**	EtO_2CCH_2Br	89
b		$PhCH_2Br$	83
c		$CH_3(CH_2)_7Br$	88
d		$CH_2=CHCH_2Br$	94
e		$Br(CH_2)_4Br$ (1 equiv.)	45[b]
		$Br(CH_2)_4Br$ (2 equiv.)	58[c]
f	**1b**	$CH_3(CH_2)_7Br$	73

(a) Yield of isolated product after purification by column chromatography. (b) With 23% of dialkylated product. (c) With 5% of dialkylated product.

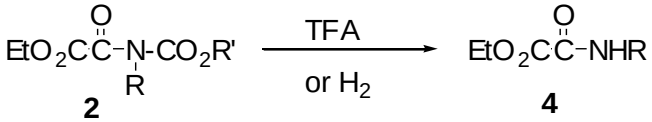
As we have previously reported,[1] access to N-protected amines from oxamates **2** was particularly easy. For example, treatment of **2c,e** with LiOH at room temperature for 3 hours gave the known carbamates **3c**[5]**,e**[6] (91,99% yield; Scheme 4).



2 **3**

Scheme 4

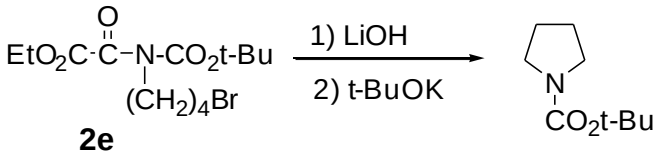
Access to free amines from carbamates **3,** by action of trifluoroacetic acid (R'= t-Bu) or catalytic hydrogenation (R'= CH_2Ph), is well known. Alternatively, deprotection of .carbamates **2** gave N-alkyl oxamates **4** (Scheme 5).



2 **4**

Scheme 5

Successive treatment of bromoalkyl compound **2e** with LiOH and t-BuOK was an interesting process for the synthesis of the N-Boc pyrrolidine **5**[7] (68% overall yield; Scheme 6)**.**



2e **5**

Scheme 6

In summary, the results described above demonstrate that N-protected ethyl oxamates **1** are excellent nitrogen nucleophiles in Gabriel reactions. Particularly mild conditions can be used to finally obtain the protected N-Boc and N-CBz amines.

Experimental

^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker AC 300 spectrometer, in $CDCl_3$ solutions with Me_4Si as internal reference. Chemical shifts are expressed in ppm and coupling constants *J* are given in Hz. DMF was distilled over $MgSO_4$. Elemental analyses were performed by the Microanalytical Laboratory of the Centre National de la Recherche Scientifique, Gif sur Yvette. Mass spectra were taken on a Varian MAT 311 spectrometer.

Ethyloxalyl isocyanate[4] :

In a 3-neck round-bottom flask equipped with a reflux condenser and a $CaCl_2$ drying tube, a solution of ethyl oxamate (40 g, 0.34 mol) in 1,2-dichloroethane (100 mL) was treated with oxalyl chloride (36 mL, 0.41 mol) at 0°C. The mixture was refluxed during 5 h. The residue was distilled under reduced pressure. After removing oxalyl chloride and 1,2-dichloroethane under a pressure of 100 mm Hg, 40 g of ethyloxalyl isocyanate was collected (82% yield); bp 65-68°C/0.5 mm Hg.

This compound is very sensitive to moisture and should be stored at 0°C under nitrogen. ^{1}H NMR δ 1.37 (t, *J* 7, 3H); 4.37 (q, *J* 7, 2H).

N-protected ethyl oxamates 1. General procedure :

To a solution of ethyloxalyl isocyanate (2.86 g, 20 mmol) in toluene (16 mL) was added dropwise a solution of alcohol (23 mmol) in toluene (4mL) at 0°C, under nitrogen. The mixture was heated at 40°C for 15 min. After elimination of the solvent, **1** was obtained in quantitative yield and was used without further purification in reactions with bromide reagents.

N-t-butoxycarbonyl ethyl oxamate 1a :

^{1}H NMR δ 1.39 (t, *J* 7, 3H); 1.52 (s, 9H); 4.39 (q, *J* 7, 2H); 8.76 (broad, NH); ^{13}C NMR δ 13.42; 27.39; 63.23; 83.19; 148.49; 151.01; 159.25. Anal. calcd. for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found : C, 49.69; H, 6.74; N, 6.43.

N-benzyloxycarbonyl ethyl oxamate 1b :

^{1}H NMR δ 1.35 (t, *J* 7, 3H); 4.35 (q, *J* 7, 2H); 5.22 (s, 2H); 7.37 (m, 5H); 9.01 (broad, NH) ; ^{13}C NMR δ 13.46; 63.62; 68.07; 128.24; 128.36; 128.47; 134.23; 150.00; 152.04; 158.97. HRMS calcd for $C_{12}H_{13}NO_5$: 251.0794 (M^+); found : 251.0796.

N-protected N-alkyl ethyl oxamates 2. General procedure :

To a solution of **1** (3 mmol) in dry DMF (5 mL) was added potassium t-butoxide

(336 mg, 3 mmol) and bromide reagent (2.3 mmol). The solution was heated at 60°C for 1 h. After addition of CH_2Cl_2 (10 mL) to the mixture, the organic layer was washed with water (2x10 mL), dried over sodium sulfate and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography on silica gel using ethylacetate/cyclohexane (1/4) as eluent and gave **2a-f.**

N-t-butoxycarbonyl N-ethylacetate ethyl oxamate 2a :

^{1}H NMR δ 1.43 (t, *J* 7, 3H); 1.52 (t, *J* 7, 3H); 1.65 (s, 9H); 4.37 (q, *J* 7, 2H); 4.51 (q, *J* 7, 2H); 4.54 (s, 2H); ^{13}C NMR δ 14.10; 14.42; 27.96;

58.58; 44.08; 61.95

; 62.60; 86.18; 151.06; 161.60; 163.14; 167.77. HRMS calcd for $C_9H_{12}NO_7$: 246.0614 (M^+ - C_4H_9); found : 246.0618.

N-t-butoxycarbonyl N-benzyl ethyl oxamate 2b :

^{1}H NMR δ 1.35 (t, *J* 7, 3H); 1.41 (s, 9H); 4.34 (q, *J* 7, 2H); 4.83 (s, 2H); 7.38 (m, 5H); ^{13}C NMR δ 13.75; 27.63; 46.13; 62.13; 85.28; 127.58; 127.76; 128.44; 136.33; 151.52; 161.74; 163.37.; 62.60; 86.18; 151.06; 161.60; 163.14; 167.77. HRMS calcd for $C_{11}H_{13}NO_3$: 207.0895 (M^+ - C_5H_8O); found : 207.0899.

N-t-butoxycarbonyl N-octyl ethyl oxamate 2c :

^{1}H NMR δ 0.81 (t, *J* 7, 3H); 1.21-1.23 (m, 12H); 1.29 (t, *J* 7, 3H); 1.45 (s, 9H); 3.58 (t, *J* 7.5, 2H); 4.27 (q, *J* 7, 2H); ^{13}C NMR δ 13.64; 13.91; 22.47; 26.50; 27.62 ; 27.97; 28.99; 31.60; 43.06; 61.83; 84.70; 151.62; 161.80; 163.16. HRMS calcd for $C_{13}H_{23}NO_5$: 273.1576 (M^+ - C_4H_8); found : 273.1567.

N-t-butoxycarbonyl N-prop-2-enyl ethyl oxamate 2d :

^{1}H NMR δ 1.28 (t, *J* 7, 3H); 1.43 (s, 9H); 4.17-4.19 (dxt, ^{2}J 1.4,^{3}J 5.6, 2H); 4.27 (q, *J* 7, 2H); 5.09-5.17 (m, 2H); 5.69-5.78 (m, 1H); ^{13}C NMR δ 13.49; 27.41; 44.70 ; 61.75; 84.81; 117.18; 131.34; 151.16; 161.45; 162.66. HRMS calcd for $C_{12}H_{19}NO_5$: 257.1263 (M^+); found : 257.1263.

N-t-butoxycarbonyl N-4-bromobutyl ethyl oxamate 2e :

^{1}H NMR δ 1.32 (t, *J* 7, 3H); 1.48 (s, 9H); 1.66-1.90 (m, 4H); 3.39 (t, *J* 6.5, 2H); 3.66 (t, *J* 6.5, 2H); 4.30 (q, *J* 7, 2H); ^{13}C NMR δ 14.13; 27.07; 28.09; 30.04; 33.29 ; 42.44; 63.38; 85.58; 151.87; 162.04; 163.63. HRMS calcd for $C_9H_{22}NO_5Br$: 295.0055 (M^+ - C_4H_8); found : 295.0053.

N-benzyloxycarbonyl N-octyl ethyl oxamate 2f :

^{1}H NMR δ 1.07 (t, *J* 7, 3H); 1.42-1.52 (m, 12H); 1.74 (m, 3H); 3.90 (t, *J* 7.5, 2H); 4.35 (q, *J* 7, 2H); 5.44 (s, 2H); 7.57 (m, 5H); ^{13}C NMR δ 14.12; 14.47; 23.01; 26.95; 28.17; 29.12; 32.13; 43.68; 62.58; 69.86; 129.03; 129.13; 129.35; 134.55 ; 153.68; 162.14; 163.58. HRMS calcd for $C_{20}H_{29}NO_5$: 363.2046 (M^+); found : 363.2044.

N-alkyl t-butyl carbamates 3. General procedure :

To a solution of **2** (2 mmol) in THF (4 mL) was added a solution of LiOH (6 mmol) in H_2O (3 mL) at room temperature. After 3 h, the reaction mixture was

diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and concentrated in vacuo to give **3**.

N-octyl t-butyl carbamate 3c[5] :

99% yield. ^{1}H NMR δ 0.83 (t, *J* 7, 3H); 1.22 (s, 9H); 1.32–1.47 (m, 12H); 3.05 (q, *J* 7, 2H); 4.58 (broad, NH); ^{13}C NMR δ 14.00; 22.56; 26.82; 28.42; 29.23; 29.27; 30.08; 31.79; 40.62; 78.80; 155.93.

N-4-bromobutyl t-butyl carbamate 3e[6] :

91% yield. ^{1}H NMR δ 1.38 (s, 9H); 1.52-1.62 (m, 2H); 1.78-1.88 (m, 2H); 3.09 (t, *J* 6.5, 2H); 3.36 (t, *J* 6.5, 2H); 4.68 (broad, NH); ^{13}C NMR δ 28.26; 28.61; 29.78; 33.17; 39.40; 79.00; 155.87.

N-octyl ethyl oxamate 4c :

To a solution of **2c** (329 mg, 1 mmol) in dichloromethane (2 mL) was added TFA (3.11 mL, 40 mmol) at room temperature. After 3 h, the crude reaction mixture was washed with Na_2CO_3 10% (5 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give **4c** (86% yield).

^{1}H NMR δ 0.81 (t, *J* 7, 3H); 1.11-1.31 (m, 10H); 1.32 (t, *J* 7, 3H); 1.42 –1.60 (m, 2H); 3.26 (q, *J* 7, 2H); 4.28 (q, *J* 7, 2H); 7.27 (broad, NH); ^{13}C NMR δ 13.56; 13.76; 22.36; 26.57; 28.73; 28.91; 31.52; 39.91; 63.02; 156.92; 160.26. HRMS calcd for $C_{12}H_{23}NO_3$: 229.1678 (M^+); found : 229.1683.

N-t-butoxycarbonyl pyrrolidine 5[7] :

This compound was obtained in 75 % yield from **3e** (504 mg, 2 mmol) by using the conditions described for the preparation of the oxamates **2** .

^{1}H NMR δ 1.36 (s, 9H); 1.65-1.81 (m, 4H); 3.20 (t, *J* 7, 4H); ^{13}C NMR δ 24.79; 25.54; 28.33; 45.41; 45.73; 78.64; 154.47.

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