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Efficient 'One Pot' Nitro Reduction-Protection of γ-Nitro Aliphatic Methyl Esters

Francisco D. Díaz-Coutiño and Jaime Escalante*

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos. Av. Universidad No. 1001, Col. Chamilpa, C.P. 62210 Cuernavaca, Mor., México. Tel.: +52 (777) 3 29 79 97; fax: +52 (777) 3 29 79 98; e-mail: jaime@ciq.uaem.mx.

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Abstract. A simple and efficient protocol has been developed for the direct conversion of γ-nitro aliphatic methyl esters to *N*-(*tert*-butoxycarbonyl)amine methyl esters using $NH_4^+HCO_2^-$ and Pd/C in the presence of $(Boc)_2O$. There was a significant decrease in the reaction time under these conditions, increased yields and the purity of the products using this 'one pot' procedure.
Keywords: 'One-pot' reaction, γ-nitro reduction, *N*-Boc-amino protection.

Resumen. Un protocolo simple y eficiente de síntesis ha sido desarrollado para la conversión directa de metil ésteres de γ-nitro alifáticos a *N*-(*tert*-butoxicarbonil)amina metil ésteres empleando $NH_4^+HCO_2^-$ y Pd/C en presencia de $(Boc)_2O$. En este procedimiento 'one pot', se observó una disminución en el tiempo de la reacción, y el rendimiento y pureza de los productos fueron excelentes.
Palabras clave: Reacción 'One-pot', γ-nitro reducción, *N*-Boc-amino protección.

Introduction

'One pot' reactions are gaining prominence due to their environmental advantages and cost effectiveness. Reduction of nitro compounds are described in the literature, and these methodologies involve catalytic hydrogenations [1], activated metal catalysis [2], indium powder [3] or Ni/Raney with formic acid [4], reduction in solid phase [5], and other methodologies reported utilizing bioreductions [6,7], have been reported as efficient methods. However, some disadvantages to these methods involve high pressure, long reactions times, the use of strong acid, and in some cases the obtained γ-amino ester spontaneously cyclizes to the parent pyrrolidin-2-one [8].

Recently, two papers described the nitro reduction to amines with tin metal [9] or iron powder under ultrasonic irradiation [10], but these methods included application only to aryl nitro compounds. Motivated by the development of biocatalysts applied specifically to the resolution of racemic β-amino methyl esters [11], our research developed a procedure for the preparation of a series of γ-*N*-(*tert*-butoxycarbonyl)amine methyl esters (**10-12**) derived from nitro methyl esters (**1-3**), under 'one pot' reaction.

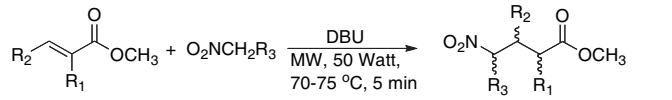
Results and discussion

Preparation of γ-nitroaliphatic methyl ester

Inspired by the reported conversion of nitroalkanes to γ-nitroaliphatic methyl ester [12,13], we treated methyl acrylates (**1-3**) with nitroalkanes in the presence of DBU under microwave irradiation [14,15]. Under these conditions the desired γ-nitroaliphatic methyl esters (**4-6**) were obtained in excellent yields, in contrast with conventional heating (Scheme 1).

Preparation of γ-Boc-amino methyl ester

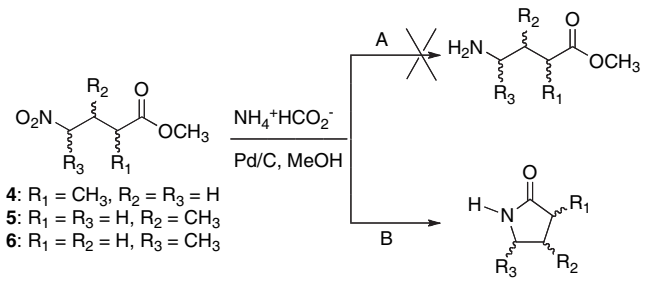
However, reduction of the nitro group using Pd/C, $NH_4^+HCO_2^-$ [16] did not provide the free γ-amino methyl ester (pathway A in Scheme 2). Instead, we have observed formation of the corresponding pyrrolidin-2-ones (**7-9**) resulting from a tandem cyclization of the putative free amines (pathway B in Scheme 2) [8].



1: $R_1 = CH_3$, $R_2 = H$ $R_3 = H$
2: $R_1 = H$, $R_2 = CH_3$ $R_3 = H$
3: $R_1 = R_2 = H$ $R_3 = CH_3$

4: $R_1 = CH_3$, $R_2 = R_3 = H$, 70 %
5: $R_1 = R_3 = H$, $R_2 = CH_3$, 95 %
6: $R_1 = R_2 = H$, $R_3 = CH_3$, 80%

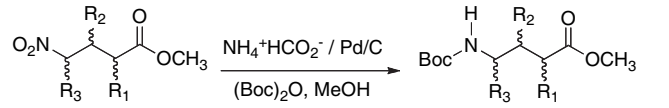
Scheme 1.



4: $R_1 = CH_3$, $R_2 = R_3 = H$
5: $R_1 = R_3 = H$, $R_2 = CH_3$
6: $R_1 = R_2 = H$, $R_3 = CH_3$

7: $R_1 = CH_3$, $R_2 = R_3 = H$, 71 %
8: $R_1 = R_3 = H$, $R_2 = CH_3$, 57 %
9: $R_1 = R_2 = H$, $R_3 = CH_3$, 25 %

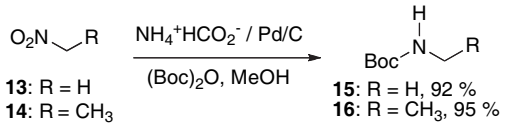
Scheme 2.



4: $R_1 = CH_3$, $R_2 = R_3 = H$
5: $R_1 = R_3 = H$, $R_2 = CH_3$
6: $R_1 = R_2 = H$, $R_3 = CH_3$

10: $R_1 = CH_3$, $R_2 = R_3 = H$, 85 %
11: $R_1 = R_3 = H$, $R_2 = CH_3$, 90 %
12: $R_1 = R_2 = H$, $R_3 = CH_3$, 80 %

Scheme 3.



13: R = H
14: $R = CH_3$

15: R = H, 92 %
16: $R = CH_3$, 95 %

Scheme 4.

In order to explore the scope of reduction of nitro compounds and trapping the amines as carbamates in 'one pot' reaction to avoid cyclization, we carried out the reaction of γ-nitroaliphatic methyl ester (**4**-**6**), using Pd/C, $NH_4^+HCO_2^-$, and di-*tert*-butyl dicarbonate in methanol (Scheme 3). Interestingly, TLC analysis of the reaction crude, after 1 h, showed complete consumption of starting material. Column chromatography of the reaction mixture afforded γ-*N*-(*tert*-butoxycarbonyl)amine methyl esters (**10**-**12**) in 80-90 % yields.

Additionally, this metodology was applied to nitrometane and nitroethane, and after 1 h of reaction, TLC analysis demonstrated that the starting material was consumed. The purification by column chromatography afforded the *tert*-butyl methylcarbamate (**15**) and *tert*-butyl ethylcarbamate (**16**) in excellent yields (Scheme 4).

Conclusions

In conclusion, we have established a novel and efficient protocol for direct conversion of nitro methyl esters to *N*-Boc-protected amine methyl esters, under neutral conditions in short reaction times. The 'one pot' conversion described here has application in multiple-step organic synthesis such as preparation of GABA analogues which can be resolved using enzymatic methods through transesterification catalyzed by CALB [11]. We are currently working on this effective enzymatic resolution process to prepare γ-amino methyl esters *N*-Boc-protected, the results will be publish in due course.

Experimental

General

^1H and ^{13}C-NMR spectra were obtained in $CDCl_3$ solutions with TMS as internal standard on Varian Gemini 200 or Inova 400 MHz spectrometers. Microwave reaction were performed in sealed vessels in a monomode microwave CEM Discover apparatus [17]. Methyl methacrylate (**1**), methyl crotonate (**2**), methyl acrylate (**3**), nitromethane, nitroethane, DBU, and TMG were purchased from Aldrich and used without further purification.

A) Michael Addition of nitroalkanes to methyl acrylates. γ-Nitroaliphatic methyl esters (**4**-**6**), were prepared under microwave irradiation as has been reported [14]. Only the preparation and properties of new compounds are described afterwards.

B) General procedure for the synthesis of pyrrolidin-2-one (**7**-**9**). $NH_4^+HCO_2^-$ (6.88 mmol) is added to a solution of nitro methyl esters (**4**-**6**, 0.86 mmol), with Pd/C in MeOH and the mixture is stirred for 2.5–3.5 h. The solution is then filtered with vacuum and Pd/C is washed with absolute methanol (10 mL). Pyrrolidin-2-ones (**7**-**9**) were purified by column chromatography.

(*rac*)-3-Methylpyrrolidin-2-one, (±)-**7**. Yield 71 %, after purification by FCC (Hex:AcOEt: 90:10 to 60:40). Yellow liquid, ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 6.6 Hz, CH_3), 1.50–1.70 (1H, m, CH_2CH), 2.22–2.37 (3H, m, CH_2C*H*CH_2N), 3.70–3.86 (1H, m, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 (*C*H_3), 30.2 (*C*H_2CH), 31.7 (*C*H), 64.5 (*C*H_2N), 180.6 (*C*O). Compared with lit. [18].

(*rac*)-4-Methylpyrrolidin-2-one, (±)-**8**. Yield 57 % after purification by FCC (Hex:AcOEt: 90:10 to 60:40). Yellow liquid; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.6 Hz, CH_3), 1.94–2.05 (1H, dd, J = 5.0, 15.4 Hz, CH_2CH), 2.4–2.61 (2H, m, CH_2C*H*), 3.18–3.26 (1H, dd , J = 5.8, 7.5 Hz, CH_2N), 3.69–3.78 (1H, dd, J = 8.2 Hz, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5 (*C*H_3), 24.3 (*C*H), 37.1 (*C*H_2CH), 56.4 (*C*H_2N), 170.1 (*C*O). Compared with lit. [18].

(*rac*)-5-Methylpyrrolidin-2-one, (±)-**9**. Yield 25 %, after purification by FCC (Hex:AcOEt: 90:10 to 60:40). Yellow liquid; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 6.2 Hz, CH_3), 1.60–1.71 (1H, m, CH_2CH$_2$), 2.18–2.40 (3H, m, CH_2CH_2C*H*N), 3.68–3.91 (1H, m, C*H*N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4 (*C*H_3), 29.3(*C*H_2CH), 30.8(*C*H_2CO), 50.4 (*C*H), 178.6 (*C*O). Compared with lit. [18].

C) General procedure for synthesis of γ-N-(tert-butoxycarbonyl)amine methyl esters (**10**-**12**). A mixture of γ-nitro methyl esters (**4**-**6**, 0.86 mmol), $(Boc)_2O$ (0.94 mmol), $NH_4^+HCO_2^-$ (6.88 mmol), and Pd/C (112 mg, 5 %) in MeOH (5 mL) was stirred for 1 h. At the end of the reaction the mixture was filtered over a pad of celite, washed with MeOH (10 mL) and concentrated on a rotatory evaporator. The residue was redissolved in 10 mL of water and extracted with EtOAc (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give the crude product. Which after

flash chromatography yielded γ-*N*-(*tert*-butoxycarbonyl)amines (**10**-**12**) [18].

(*rac*)-Methyl 4-*N*-(*tert*-butoxycarbonyl)amine-2-methylbutanoate (±)-**10**. Yield 85 %, after purification by FCC (Hex: AcOEt: 95:10 to 70:30). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 6.6 Hz, CH_3), 1.44 (9H, s, [(CH_3)$_3$C], 1.58–1.89 (3H, m, CH_2CHCH_2N), 2.37 (2H, t , *J* = 7.8 Hz, CH_2N), 3.67 (3H, s, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5 (*C*H$_3$), 28.5 [(*C*H$_3$)$_3$C], 31.0 (*C*HCH$_2$), 32.3 (*C*HCH$_3$), 51.7 (*C*H$_2$N), 54.5 (*C*H$_3$O), 85.8 (CH$_3$)$_3$*C*), 170.8 (*C*OBoc), 174.0 (*C*OOCH$_3$). HRMS (FAB): calcd for $[M+H]^+$ $C_{11}H_{22}NO_4$: 232.1549; found: 232.1556.

(*rac*)-Methyl 4-*N*-(*tert*-butoxycarbonyl)amine-3-methylbutanoate (±)-**11**. Yield 90 %, after purification by FCC (Hex: AcOEt: 95:10 to 70:30). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 6.6 Hz, CH_3), 1.46 [9H, s, (CH_3)$_3$C] 2.2 (1H, dd, *J* = 17.5, 9.0 Hz, CH_2CH), 2.32-2.53 (2H, m, CH_2CH), 3.23–3.52 (2H, m,CH_2N), 3.67 (3H, s, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (*C*H$_3$), 28.4 [(*C*H$_3$)$_3$C], 28.8 (*C*HCH$_3$), 39.0 (CH*C*H$_2$), 51.7 (*C*H$_2$N), 55.8 (*C*H$_3$O), 81.5 (CH$_3$)$_3$*C*), 156.7 (*C*OBoc), 173.9 (*C*OOCH$_3$). HRMS (FAB): calcd for $[M+H]^+$ $C_{11}H_{22}NO_4$: 232.1549; found: 232.1579.

(*rac*)-Methyl 4-*N*-(*tert*-butoxycarbonyl)amine pentanoate (±)-**12**. Yield 85 % after purification by FCC (Hex:AcOEt: 95:10 to 70:30). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 6.6 Hz, CH_3), 1.44 [9H, s, (CH_3)$_3$C], 1.60–1.89 (2H, m, CH_2CH), 2.37 (2H, t, *J* = 7.7 Hz, CH_2CO), 3.46-3.59 (1H, m, CHCH$_3$), 3.68 (3H, s, CH_3O). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6 (*C*H$_3$), 28.6 [(*C*H$_3$)$_3$C], 31.1 (*C*HCH$_3$), 32.4 (CH*C*H$_2$), 46.5 (*C*HN), 51.8 (*C*H$_3$O), 79.6 [(CH$_3$)$_3$*C*] 155.5 (*C*OBoc), 174.1 (*C*OOCH$_3$). HRMS (FAB): calcd for $[M+H]^+$ $C_{11}H_{22}NO_4$: 232.1549; found: 232.1568.

tert-butyl methylcarbamate (**15**). Yield 92 %, after purification by FCC (Hex:EtOAc: 95:10 to 80:20). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (9H, s, (CH_3)$_3$C), 3.16 (3H, s, CH_3N). ^{13}C NMR (50 MHz, $CDCl_3$) 28.5 [(*C*H$_3$)$_3$C], 38.3 (*C*H$_3$N), 81.8 (CH$_3$)$_3$*C*), 157.8 (*C*OBoc).

tert-butyl ethylcarbamate (**16**). Yield 95 %, after purification by FCC (Hex:AcOEt: 95:10 to 80:20). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, t, *J* = 7.2 Hz, CH_3CH$_2$), 1.48 (9H, s, (CH_3)$_3$C), 3.52 (2H, q, *J* = 7.0 Hz, CH$_3$CH_2), ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.3 (*C*H$_3$CH$_2$), 28.5 [(*C*H$_3$)$_3$C], 45.6 (*C*H$_2$CH$_3$), 81.6 [(CH$_3$)$_3$*C*], 157.3 (*C*OBoc).

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