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Tetrahedron Letters 45 (2004) 5121–5124
Tetrahedron Letters

Nitrobenzylation of α-carbonyl ester derivatives using TDAE approach

Gamal Giuglio-Tonolo,[a] Thierry Terme,[a] Maurice Médebielle[b] and Patrice Vanelle[a,*]

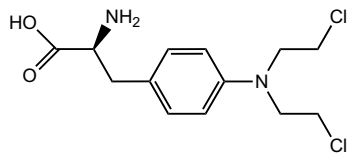
[a]*Laboratoire de Chimie Organique Pharmaceutique LCOP, UMR CNRS 6517, Université de la Méditerranée, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France*
[b]*Université Claude Bernard-Lyon 1, Laboratoire SERCOF, UMR CNRS 5181, Bâtiment E. Chevreul, 43, Bd du 11 novembre 1918, F-69622 Villeurbanne, France*

Received 18 March 2004; revised 1 April 2004; accepted 28 April 2004

Abstract—A series of 2-hydroxy-propionic acid ethyl ester derivatives was prepared in good yields by reaction of *o*- and *p*-nitrobenzyl chlorides (**1**, **8**) with various α-carbonyl esters in presence of tetrakis(dimethylamino)ethylene (TDAE). This reaction was generalized to α-ketolactam and α-ketomalonate.

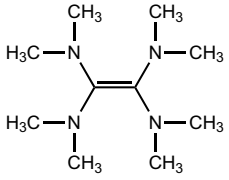
Melphalan or 2-amino-3-{4-[bis-(2-chloroethyl)-amino]-phenyl}-propionic acid was synthesized in the 1950s as one of a series of nitrogen mustard derivatives (Scheme 1).[1] Drugs of this class are clinically important anticancer agents.[2] Melphalan, also known as L-phenylalanine mustard is used systemically in treatment of patients with multiple myeloma, ovarian cancer, breast cancer, melanoma, and colorectal cancer.[3] It is also employed 'locally' in isolated perfusion of the limb (melanoma of the upper or lower limb)[4] or the liver (metastases confined to the liver).[5]

However, melphalan, especially at high dose, shows a diversity of toxic side effects.[3] The most common side effect occurring during therapy is bone marrow suppression, including leukopenia, and thrombocytopenia. Of serious concern is the carcinogenic potential of melphalan: secondary malignancies, such as acute non-lymphocytic leukemia, myeloproliferative syndrome, and carcinoma have been reported in patients treated with melphalan.[3] In order to minimize the side effects, efforts were undertaken to construct new prodrugs.[6]



Scheme 1. Structure of melphalan.

Tetrakis(dimethylamino)ethylene (TDAE, Scheme 2) is a reducing agent, which reacts with halogenated derivatives to generate under mild conditions an anion via a single electron transfer (SET).[7] We have recently shown that from *p*-nitrobenzyl chloride, TDAE could generate a nitrobenzyl carbanion, which is able to react with various electrophiles as aromatic aldehydes.[8] Moreover, we have shown that halogenodifluoromethyl heterocycles react with ethyl pyruvate using TDAE methodology to form 3,3-difluoro-2-hydroxy-2-methyl-4-oxo-butyric acid ethyl ester derivatives.[9]



Scheme 2. Structure of TDAE.

Keywords: TDAE; *p*-Nitrobenzyl chloride; α-Carbonyl ester; α-Hydroxy ester.

* Corresponding author. Tel.: +33-4-9183-5580; fax: +33-4-9179-4677; e-mail: patrice.vanelle@pharmacie.univ-mrs.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.166

In continuation of our program directed toward the study of single electron transfer (SET) reactions[10] of bioreductive alkylating agents and the development of novel melphalan derivatives as potential antineoplastic agents, we report herein the reaction of *p*-nitrobenzyl chloride with α-carbonyl esters using TDAE leading to 2-hydroxy-3-phenyl-propionic acid ethyl ester derivatives. These compounds could be suitable intermediates of the synthesis of melphalan analogs by reduction of nitro group followed by *N*-alkylation and hydrolysis of ester function leading to α-hydroxy acid derivatives.

The reaction of *p*-nitrobenzyl chloride (**1**) with 3 equiv of α-carbonyl esters (**2**–**4**) in presence of TDAE at −20 °C for 1 h followed by 2 h at room temperature led to the corresponding α-hydroxy esters (**5**–**7**) in good yields (60–73%) as shown in Table 1 (Scheme 3).[11] The formation of these α-hydroxy esters (**5**–**7**) may be explained by nucleophilic addition of nitrobenzyl carbanion, formed by action of TDAE with *p*-nitrobenzyl chloride (**1**), on carbonyl group of α-carbonyl esters (**2**–**4**). The good yields observed with *p*-nitrobenzyl chloride (**1**) encouraged us to study the reactivity of *o*-nitrobenzyl chloride (**8**) with the same α-carbonyl esters (**2**–**4**). In the same reaction conditions (TDAE at −20 °C for 1 h followed by 2 h at room temperature) with α-carbonyl esters (**2-4**), the *o*-nitrobenzyl chloride (**8**) furnished the corresponding α-hydroxy esters (**9**–**11**) in 66–80% yields (Table 1). This method using TDAE presents a great synthetic interest, as compared to benzylation reaction using organometallic compounds;[13] TDAE methodology is a regioselective method with carbonyl esters, only the carbonyl group reacts with nitrobenzyl anion. We have never observed the reaction of nitrobenzyl anion with ester moiety.

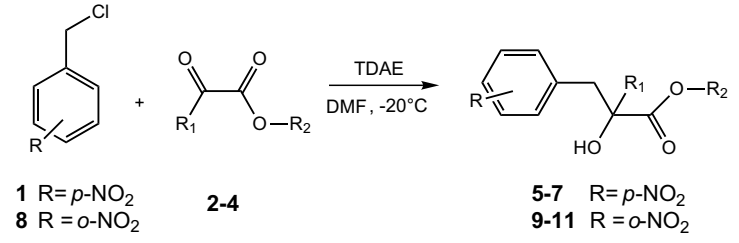
In order to generalize this reaction, we have investigated the action of *o*- and *p*-nitrobenzyl anions with similar carbonyl structures (α-ketolactam or ketomalonate). The reaction of *p*-nitrobenzyl chloride (**1**) with 1-methyl isatin (**12**) in presence of TDAE furnished the corresponding α-hydroxy lactam (**13**) in 62% yield (Scheme 4). In the same conditions, the reaction of *o*- and *p*-nitrobenzyl chlorides (**1** or **8**) with diethyl ketomalonate (**14**) gave the corresponding 2-hydroxy-2-nitrobenzyl malonic acid diethyl ester (**15**–**16**) in respectively, 45% and 81% yields (Scheme 5).

In conclusion, we have showed that *o*- or *p*-nitrobenzyl chlorides and α-carbonyl esters react using TDAE to prepare new α-hydroxy ester derivatives in good yields. This method, using TDAE, is an easy, original, and mild method to prepare *p*-nitrobenzyl anion in situ, compared to the classical method using organometallic compounds.[13] Moreover, this method was generalized to α-ketolactam and ketomalonate derivatives. The prepa-

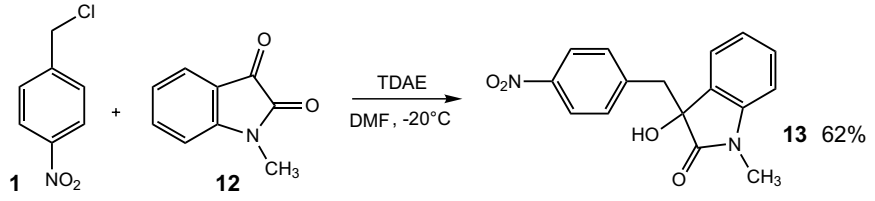
Table 1. Reaction of *o*- or *p*-nitrobenzyl chloride and α-carbonyl esters using TDAE[a]

Nitrobenzyl chloride	α-Carbonyl ester	R_1	R_2	α-Hydroxy ester	Yield (%)[b]
1	**2**	H	CH_2CH_3	**5**	60
1	**3**	CH_3	CH_2CH_3	**6**[12]	73
1	**4**	CF_3	CH_3	**7**	73
8	**2**	H	CH_2CH_3	**9**	71
8	**3**	CH_3	CH_2CH_3	**10**	80
8	**4**	CF_3	CH_3	**11**	66

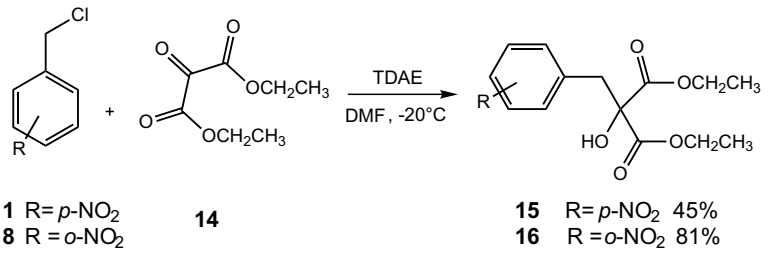
[a] All the reactions are performed using 3 equiv of α-carbonyl ester (**2**–**4**), 1 equiv of chloride (**1** or **8**), and 1 equiv of TDAE in anhydrous DMF.
[b] % Yield relative to chloride (**1** or **8**).



Scheme 3. Reaction of *o*- or *p*-nitrobenzyl chloride and α-keto esters using TDAE.



Scheme 4. Reaction of **1** and 1-methyl isatin **12** using TDAE.



Scheme 5. Reaction of **1** or **8** with diethyl ketomalonate **14** using TDAE.

ration of α-hydroxy acid analogs of melphalan (reduction of nitro, alkylation, and hydrolysis) and the pharmacological evaluation of all intermediates are under active investigation.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique. We express our thanks to M. Noailly for ^{1}H and ^{13}C NMR spectra recording.

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11. General procedure for the reaction of *p*-nitrobenzyl chloride (**1** or **8**) and carbonyl esters (**2**–**4**), ketolactam (**12**) and ketomalonate (**14**) using TDAE. Into a two-necked flask equipped with a silica gel drying tube and a nitrogen inlet was added, under nitrogen at −20 °C, 7 mL of anhydrous DMF solution of **1** (0.52 g, 3 mmol) and corresponding carbonyl derivatives **2**–**6** (9 mmol, 3 equiv). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.60 g, 3.3 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to room temperature for 2 h. After this time TLC analysis (dichloromethane) clearly showed that **1** or **8** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with toluene (3×40 mL), the combined organic layers washed with H_2O (3×40 mL), and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography (dichloromethane) and recrystallization from hexane/ethanol (9/1) gave the corresponding α-hydroxy derivatives. New products: **5**; orange solid; mp 36 °C, ^{1}H NMR ($CDCl_3$): δ 1.30 (t, $J = 7.2$ Hz, 3H); 2.93 (d, $J = 5.1$ Hz, 1H); 3.05 (dd, $J_{AB} = 14.0$ Hz and $J = 6.9$ Hz, 1H); 3.24 (dd, $J_{AB} = 14.0$ Hz and $J = 4.3$ Hz, 1H); 4.24 (q, $J = 7.2$ Hz, 2H); 4.46 (m, 1H); 7.41 (d, $J = 8.6$ Hz, 2H); 8.15 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.0; 37.2; 62.1; 70.3; 124.8; 127.9; 131.7; 132.7; 133.2; 149.9; 174.0. Anal. Calcd for $C_{11}H_{13}NO_5$ (239.22): C, 55.23; H, 5.48; N, 5.86. Found: C, 55.19; H, 5.51; N, 5.55. **7**; white solid; mp 121 °C, ^{1}H NMR ($CDCl_3$): δ 3.28 (d, $J_{AB} = 13.8$ Hz, 1H); 3.39 (d, $J_{AB} = 13.8$ Hz, 1H); 3.82 (bs, 1H); 3.85 (s, 3H); 7.42 (d, $J = 8.9$ Hz, 2H); 8.16 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 37.2; 54.3; 78.2; 123.1; 123.4; 131.3; 140.5; 147.6; 168.9. Anal. Calcd for $C_{11}H_{10}F_3NO_5$ (293.20): C, 45.06; H, 3.44; N, 4.78. Found: C, 45.01; H, 3.18; N, 4.81. **9**; colorless oil, ^{1}H NMR ($CDCl_3$): δ 1.28 (t, $J = 7.2$ Hz, 3H); 2.93 (d, $J = 5.6$ Hz, 1H); 3.20 (dd, $J_{AB} = 13.8$ Hz and

$J = 8.3$ Hz, 1H); 3.54 (dd, $J_{AB} = 13.8$ Hz and $J = 4.3$ Hz, 1H); 4.24 (q, $J = 7.2$ Hz, 2H); 4.49 (m, 1H); 7.36–7.59 (m, 3H); 7.90–7.94 (m, 1H). ^{13}C NMR ($CDCl_3$) 14.0; 37.2; 62.1; 70.3; 124.8; 127.9; 131.7; 132.7; 133.2; 149.9; 174.0. Anal. Calcd for $C_{11}H_{13}NO_5$ (239.22): C, 55.23; H, 5.48; N, 5.86. Found: C, 54.93; H, 5.41; N, 5.91. **10**; white solid; mp 43 °C, ^{1}H NMR ($CDCl_3$): δ 1.27 (t, $J = 7.2$ Hz, 3H); 1.44 (s, 3H); 3.21 (bs, 1H); 3.46 (s, 2H); 4.17 (q, $J = 7.2$ Hz, 2H); 7.33–7.53 (m, 3H); 7.78–7.82 (m, 1H). ^{13}C NMR ($CDCl_3$) 14.0; 26.2; 40.6; 62.3; 74.8; 124.5; 127.9; 130.4; 132.0; 133.2; 151.1; 175.9. Anal. Calcd for $C_{12}H_{15}NO_5$ (253.25): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.61; H, 6.00; N, 5.54. **11**; white solid; mp 89 °C, ^{1}H NMR ($CDCl_3$): δ 3.75 (s, 2H); 3.83 (s, 3H); 3.93 (bs, 1H); 7.38–7.57 (m, 3H); 7.80–7.85 (m, 1H). ^{13}C NMR ($CDCl_3$) 32.8; 54.4; 77.2; 123.1; 124.8; 127.2; 128.8; 132.3; 133.2; 151.1; 169.1. Anal. Calcd for $C_{11}H_{10}F_3NO_5$ (293.20): C, 45.06; H, 3.44; N, 4.78. Found: C, 45.01; H, 3.18; N, 4.81. **13**; yellow solid; mp 193 °C, ^{1}H NMR ($CDCl_3$): δ 3.03 (s, 3H); 3.26 (d, $J_{AB} = 12.8$ Hz, 1H); 3.37 (d, $J_{AB} = 12.8$ Hz, 1H); 3.78 (b s, 1H); 6.68 (d, $J = 7.8$ Hz, 1H); 7.04–7.33 (m, 3H); 7.13 (d, $J = 8.7$ Hz, 2H); 7.98 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 26.1; 44.4; 77.1; 108.6; 122.9; 123.2; 124.3; 128,6; 130.1; 131.0; 131.1; 141.9; 142.9; 147.0; 177.5. Anal. Calcd for $C_{16}H_{14}N_2O_4$ (298.29): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.38; H, 4.80; N, 9.26. **15**; white solid; mp 57 °C, ^{1}H NMR ($CDCl_3$): δ 1.28 (t, $J = 7.2$ Hz, 6H); 3.44 (s, 2H); 3.82 (bs, 1H); 4.25 (q, $J = 7.2$ Hz, 4H); 7.44 (d, $J = 8.8$ Hz, 2H); 8.13 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.0; 39.9; 62.9; 78.7; 123.1; 131.3; 142.5; 147.2; 169.4. Anal. Calcd for $C_{14}H_{17}NO_7$ (311.29): C, 54.02; H, 5.50; N, 4.50. Found: C, 54.16; H, 5.50; N; 4.54. **16**; pale yellow solid; mp 47 °C, ^{1}H NMR ($CDCl_3$): δ 1.25 (t, $J = 7.1$ Hz, 6H); 3.79 (bs, 1H); 3.80 (s, 2H); 4.21 (q, $J = 7.1$ Hz, 4H); 7.33–7.49 (m, 3H); 7.77–7.81 (m, 1H). ^{13}C NMR ($CDCl_3$) 13.8; 35.2; 62.8; 78.7; 124.5; 128.1; 129.0; 132.0; 133.1; 151.2; 169.4. Anal. Calcd for $C_{14}H_{17}NO_7$ (311.29): C, 54.02; H, 5.50; N, 4.50. Found: C, 53.53; H, 5.44; N; 4.14.

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