Derivatives. Enhanced Stereoselectivity Observed for the Conjugate Addition Reaction of Phenylmagnesium Bromide Derivatives with Anhydro Dichloromethane

Lifen Xu and Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans. LA 70148
Received April 1, 1996

The use of dichloromethane as a solvent for the conjugate addition reaction of preformed etheral solutions of phenylmagnesium bromide derivatives with anhydroecgonine methyl ester (2) was found to enhance the stereoselectivity of the reaction and provide the 2β-carbomethoxy-3β-phenyltropane derivatives 3a-d in high yield.

The 2β-carbomethoxy-3β-substituted-phenyltropane derivatives have been shown to be important tools for the study of the structure-activity relationships of cocaine (1) at cocaine receptors on biogenic amine uptake sites [1-6]. These analogs of cocaine have proven to be useful as biological probes [1-4], radiolabled receptor ligands [2,5] and precursors for the synthesis of more complex cocaine receptor ligands [6,7]. However, similar to cocaine, only the 2β-isomers exhibit pharmacological activity while the 2α-isomers are inactive [1-4]. Therefore, the stereoselective synthesis of 2β-carbomethoxy-3β-phenyltropane derivatives has been the subject of several recent studies [2,3,5].

The first synthesis of 2β-carbomethoxy-3β-phenyltropane (3a) was reported by Clark *et al.* [1]. This was achieved by the conjugate addition of phenylmagnesium bromide to (R)-(–)-anhydroecgonine methyl ester (2) in ether at -20°. Under these conditions the 2β-isomer 3a was isolated as a minor product, while the 2α-isomer 4a was found to be a major product (3a:4a, 1:3). More recent studies by Neumeyer *et al.* [2], Carroll *et al.* [3], and Meltzer *et al.* [5] have shown that the stereoselectivity for the 2β-isomers could be improved by adjusting the reaction temperature and/or performing a low temperature acid quench of the reaction. These procedures typically afforded 2α:2β product ratios of 2:3 and furnished the 2β-isomer in yields of 11-60% depending on the aryl substituent. Herein we wish to report a modified procedure for the stereoselective synthesis of 2β-carbomethoxy-3β-phenyltropane derivatives. This new method exploits a dramatic solvent effect mediated by dichloromethane which resulted in enhanced stereochemical control of the conjugate addition.

The effects of solvent polarity and concentration (ether, THF, benzene) on the reactions of Grignard reagents with a variety of substrates has been the subject of numerous investigations [8-12]. It has been shown that variations of reagent concentration or substitution of one solvent (ether) for another (THF) can dramatically alter the course of the

reaction and lead to the formation of different products [12,13]. The stereochemistry of the Grignard reaction has been shown to be successfully controlled by intramolecular chelation as well as by the addition of chelating agents [14-16]. Moreover, it has been shown that the reaction of preformed alkylmagnesium halide etherates with carbonyl compounds in dichloromethane gave higher yields (10-20% increase) of the corresponding 1,2-addition products [17,18]. These results have prompted this investigation of the solvent effect of dichloromethane on the conjugate addition reaction of phenylmagnesium bromide derivatives with R-(–)-anhydroecgonine methyl ester (2) with the hope of obtaining higher yields of the corresponding 2β-carbomethoxy-3β-phenyltropane derivatives.
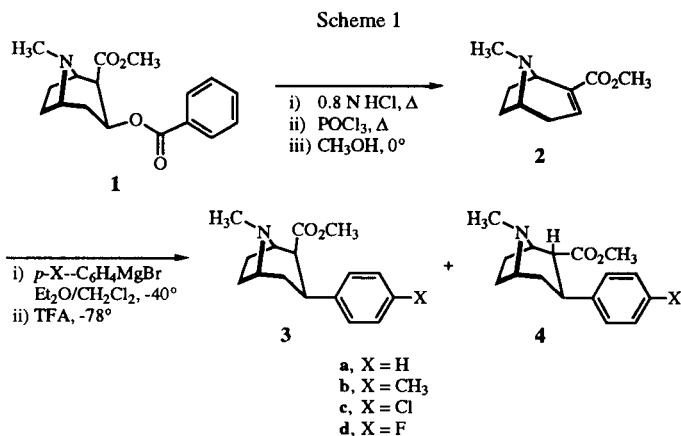
Scheme 1

As illustrated in Scheme 1, 2 could be readily obtained by the degradation of cocaine (1). This series of reactions was readily carried out on a large scale with confiscated grade cocaine [19] and provided 2 in yields of 70-90% [5]. With 2 in hand, the conjugate addition reactions of four phenylmagnesium bromide derivatives were investigated. These systems were chosen based on the relative importance of these 2β-carbomethoxy-3β-phenyltropane derivatives 3a-d for structure-activity relationships stud-

ies at the cocaine binding site [2-7]. The reactions were typically performed by the addition of a commercially available etheral solution of the Grignard reagent to a dichloromethane solution of **2** at -40° (Scheme 1). Although two equivalents of the Grignard reagent were employed in each reaction relative to **2**, no 1,2-addition products were observed under these conditions. The reaction mixture was then quenched at -78° with trifluoroacetic acid in dichloromethane *via* method A. In all cases, the overall yields of the conjugate addition products were higher than those previously obtained in ether or THF [1-6]. However, more striking was the fact that the stereoselectivity of the reaction was greatly enhanced. In all four systems, the amounts of the 2β-isomers **3a-d** were significantly greater than the 2α-isomers **4a-d** (Table 1). The isomer ratios were easily determined by

Table 1

Stereoselective Synthesis of 2β-Carbomethoxy-3β-phenyltropane Derivatives **3**

entry	X	method	3:4 [a]	Yields (%) [b]	
				3	**4**
a	H	A	5:1	71	13
b	CH$_3$	B	5:1	70	14
c	Cl	B	7:1	70	10
d	F	A	3:1	56	21

[a] Isomer ratios were determined by ^{1}H nmr. [b] Isolated yields after column chromatography.

[1]H nmr based on the chemical shift data of the *N*-methyl group. The chemical shift of the *N*-methyl signal in the 2β-isomers (~δ 2.2 ppm) was uniformly about 0.2 ppm upfield relative to the signal observed for the 2α-isomers (~δ 2.4 ppm). The 2β-isomers were easily separated from the 2α-isomers and purified by column chromatography to furnish enantiomerically pure compounds. In addition, it was found that these reactions could be performed *via* method B on a synthetically useful scale (10 g) without loss of stereoselectivity or reduction in yield.

In summary, the use of dichloromethane as a solvent for the conjugate addition reaction of preformed etheral solutions of phenylmagnesium bromide derivatives with **2** has greatly enhanced the synthetic utility of this reaction for the synthesis of 2β-carbomethoxy-3β-phenyltropane derivatives. This development will undoubtedly facilitate the synthesis of useful and new tropane derivatives for biological and pharmacological studies.

EXPERIMENTAL

Melting points were determined on a Mel-Temp II and are uncorrected. Optical rotations were determined using an Autopol

III Automatic polarimeter. All nmr spectra were recorded on a Varian-Gemini 300 MHz nmr spectrometer using tetramethylsilane (TMS) as an internal standard. All chemicals and reagents were purchased from Aldrich Chemical Company, Milwaukee, WI unless otherwise noted. The ether was dried by distillation from sodium/benzophenone and dichloromethane (E. M. Science) was dried by distillation over phosphorous pentoxide. Flash silica gel (Silica Gel 60, E. M. Science, 230-400 mesh) and tlc plates (E. M. Science, kiesel gel 60, F$_{254}$, 0.2 mm layer glassback) were purchased from Curtin Matheson Scientific. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA.

General Procedures for the Reaction of Anhydroecgonine Methyl Ester (**2**) with Phenylmagnesium Bromide Derivatives.

Method A.

A solution of substituted phenylmagnesium bromide (4 ml, 1 *M* in ether) was diluted with ether (5 ml) and added dropwise to a stirred solution of **2** (0.36 g, 2 mmoles) [5] in freshly distilled dichloromethane (5 ml) at -40° under a nitrogen atmosphere. The mixture was stirred for 3.5 hours and cooled to -78°. Trifluoroacetic acid (0.46 g, 4 mmoles) in dry dichloromethane (5 ml) was added dropwise over 10 minutes. The mixture was acidified (*p*H = 1) with concentrated hydrochloric acid and the organic layer was separated. The aqueous layer was basified (*p*H > 10) with concentrated ammonium hydroxide at 0° and was extracted with ether (4 x 30 ml). The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated. The 2α- and 2β-diastereoisomers were separated by flash column chromatography (silica gel-petroleum ether/triethylamine, 9.5:0.5, v/v).

Method B.

A solution of phenylmagnesium bromide (111 ml, 1 *M* in ether) was diluted with ether (40 ml) and added dropwise to a stirred solution of **2** (10 g, 55.3 mmoles) [5] in freshly distilled dichloromethane (100 ml) at -40° under a nitrogen atmosphere. The mixture was stirred for 3.5 hours and cooled to -78°. Trifluoroacetic acid (12.7 g, 111 mmoles) in dry dichloromethane (50 ml) was added dropwise over 20 minutes. The mixture was acidified (*p*H = 1) with concentrated hydrochloric acid and the organic layer was separated. The aqueous layer was basified (*p*H > 10) with concentrated ammonium hydroxide at 0° and was extracted with ether (4 x 300 ml). The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated. The 2α- and 2β-diastereoisomers were separated by flash column chromatography (silica gel-petroleum ether/triethylamine, 9.5:0.5, v/v).

2β-Carbomethoxy-3β-phenyltropane (**3a**).

By method A the reaction of **2** with phenylmagnesium bromide gave **3a** as a colorless oil (0.366 g, 71%), [α]$_D^{20}$ -6.94° (c 1, chloroform) [lit [1] [α]$_D^{25}$ -5.3° (c 1, chloroform)]; ^{1}H nmr (deuteriochloroform): δ 7.15-7.30 (m, 5H), 3.54 (m, 1H), 3.45 (s, 3H), 3.34 (m, 1H), 2.94-3.05 (m, 1H), 2.91 (m, 1H), 2.63 (t, J = 12.3 Hz, 1H), 2.21 (s, 3H), 2.05-2.20 (m, 2H), 1.55-1.80 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 172.2, 143.1, 128.0, 127.4, 125.9, 65.4, 62.4, 52.9, 51.2, 42.1, 34.0, 33.8, 26.1, 25.3.

2α-Carbomethoxy-3β-phenyltropane (**4a**).

By method A the reaction of **2** with phenylmagnesium bromide gave **4a** as a white solid (0.070 g, 13%), mp 70-71° (lit [1] mp 70-72°); [α]$_D^{20}$ 6.50° (c 1, chloroform); ^{1}H nmr (deuterio-

chloroform): δ 7.15-7.30 (m, 5H), 3.51 (s, 3H), 3.44 (d, J = 6.6 Hz, 1H), 3.28 (m, 1H), 3.16 (d, J = 2.8 Hz, 2H), 2.44 (s, 3H), 2.05-2.20 (m, 2H), 1.85-2.00 (m, 2H), 1.60-1.80 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 173.3, 143.6, 128.5, 127.9, 126.3, 63.7, 61.3, 53.5, 51.6, 39.6, 38.7, 36.7, 26.3, 23.1.

2β-Carbomethoxy-3β-tolyltropane (3b).

By method B the reaction of **2** with tolylmagnesium bromide gave **3b** as a colorless oil (10.7 g, 71%), $[\alpha]_D^{20}$ -0.12° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.13 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 3.52-3.58 (m, 1H), 3.49 (s, 3H), 3.37 (m, 1H), 2.92-3.04 (m, 1H), 2.88 (m, 1H), 2.52-2.65 (d t, J = 12.3 Hz, J = 2.8 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H), 2.05-2.18 (m, 1H), 1.57-1.80 (m, 4H); ^{13}C nmr (deuteriochloroform): δ 171.6, 139.5, 134.6, 128.2, 126.7, 64.9, 61.9, 52.4, 50.6, 41.6, 33.7, 33.0, 25.5, 24.8, 20.6.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.60; H, 8.50; N, 5.09.

2α-Carbomethoxy-3β-tolyltropane (4b).

By method B the reaction of **2** with tolylmagnesium bromide gave **4b** as a white solid (2.10 g, 14%), mp 104-106°; $[\alpha]_D^{20}$ 2.93° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.16 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 3.50 (s, 3H), 3.42 (m, 1H), 3.25 (t, J = 5.4 Hz, 1H), 3.12 (m, 2H), 2.42 (s, 3H), 2.29 (s, 3H), 2.1 (m, 1H), 1.83-1.98 (m, 3H), 1.57-1.79 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 173.5, 140.8, 135.9, 129.1, 127.6, 63.7, 61.2, 51.5, 51.1, 39.6, 38.7, 36.4, 26.5, 23.3, 21.1.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.51; H, 8.48; N, 5.00.

2β-Carbomethoxy-3β-(4'-chlorophenyl)tropane (3c).

By method B the reaction of **2** with 4-chlorophenylmagnesium bromide gave **3c** as a white solid (11.3 g, 70%), mp 121-123° (lit [6] mp 120-121°); $[\alpha]_D^{20}$ -3.41° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.10-7.35 (m, 4H), 3.55 (m, 1H), 3.49 (s, 3H), 2.90-3.00 (m, 1H), 2.85-3.00 (m, 1H), 2.46-2.64 (m, 1H), 2.21 (s, 3H), 2.00-2.20 (m, 2H), 1.80-1.98 (m, 1H), 1.50-1.80 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 172.2, 142.1, 131.7, 129.1, 128.3, 65.6, 62.6, 53.0, 51.5, 42.3, 34.3, 33.7, 26.2, 25.6.

2α-Carbomethoxy-3β-(4'-chlorophenyl)tropane (4c).

By method B the reaction of **2** with 4-chlorophenylmagnesium bromide gave **4c** as a colorless oil (1.62 g, 10%), $[\alpha]_D^{20}$ 0.58° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.10-7.35 (m, 4H), 3.80 (m, 1H), 3.72 (s, 3H), 3.30-3.40 (m, 1H), 3.20-3.30 (m, 1H), 3.10 (m, 1H), 2.41 (s, 3H), 2.00-2.20 (m, 2H), 1.80-1.98 (m, 1H), 1.50-1.80 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 172.9 142.7, 136.2, 129.6, 128.9, 63.7, 61.4, 58.7, 51.9, 39.3, 38.9, 36.4, 30.2, 26.5.

Anal. Calcd. for $C_{16}H_{20}NO_2Cl$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.49; H, 6.70; N, 4.91.

2β-Carbomethoxy-3β-(4'-fluorophenyl)tropane (3d).

By method A the reaction of **2** with 4-fluorophenylmagnesium bromide gave **3d** as a white solid (0.310 g, 56%), mp 88-90° (lit [1] mp 93-94.5°); $[\alpha]_D^{20}$ -39.83° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 6.90-7.00 (m, 2H), 7.17-7.27 (m, 2H), 3.57

(m, 1H), 3.50 (s, 3H), 3.36 (m, 1H), 2.97 (m, 1H), 2.87 (m, 1H), 2.58 (m, 1H), 2.23 (s, 3H), 2.06-2.20 (m, 1H), 1.55-1.79 (m, 4H); ^{13}C nmr (deuteriochloroform): δ 172.0, 139.3, 128.7, 114.7, 114.4, 65.2, 62.1, 52.8, 51.1, 41.9, 34.1, 33.1, 25.8, 25.1.

2α-Carbomethoxy-3β-(4'-fluorophenyl)tropane (4d).

By method A the reaction of **2** with 4-fluorophenylmagnesium bromide gave **3d** as a white solid (0.115 g, 21%), mp 70-72° (lit [1] mp 70.5-73°); $[\alpha]_D^{20}$ 11.11° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 6.80-7.26 (m, 4H), 3.78 (m, 1H), 3.73 (s, 3H), 3.27 (m, 1H), 2.65 (m, 1H), 2.40 (m, 1H), 2.36 (s, 3H), 2.15 (m, 2H), 1.82-1.90 (m, 2H), 1.52 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 166.2, 135.6, 129.0, 116.4, 115.1, 63.4, 58.2, 56.7, 51.4, 39.5, 35.9, 34.1, 29.8, 22.9.

REFERENCES AND NOTES

[1]   R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. Levitt, W. R. Cumiskey, and E. F. Bogado, *J. Med. Chem.*, **16**, 1260 (1973).

[2]   R. A. Milius, J. K. Saha, B. K. Madras, and J. L. Neumeyer, *J. Med. Chem.*, **34**, 1728 (1991).

[3]   F. I. Carroll, Y. Gao, M. A. Rahman, P. Abraham, K. Parham, A. H. Lewin, J. W. Boja and M. J. Kuhar, *J. Med. Chem.*, **34**, 2719 (1991).

[4]   F. I. Carroll, A. H. Lewin, J. W. Boja, and M. J. Kuhar, *J. Med. Chem.*, **35**, 969 (1992).

[5]   P. C. Meltzer, A. Y. Liang, A.-L. Brownell, D. R. Elmaleh, and B. K. Madras, *J. Med. Chem.*, **36**, 855 (1993).

[6]   A. P. Kozikowski, M. K. E. Saiah, K. M. Johnson, and J. S. Bergmann, *J. Med. Chem.*, **38**, 3086 (1995).

[7]   S. V. Kelkar, S. Izenwasser, J. L. Katz, C. L. Klein, N. Zhu, and M. L. Trudell, *J. Med Chem.*, **37**, 3875 (1994).

[8]   E. C. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 277 (1974).

[9]   H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, **31**, 1053 (1975).

[10]   E. C. Ashby and T. L. Wiesemann, *J. Am. Chem. Soc.*, **100**, 189 (1978).

[11]   C. Cianetti, G. DiMaio, V. Pignatelli, P. Tagliatesta, E. Vecchi, and E. Zeuli *Tetrahedron*, **39**, 657 (1983).

[12]   B. Miller, E. R. Matjeka, and J. G. Haggerty, *J. Org. Chem.*, **49**, 3121 (1984).

[13]   W. Schmid and G. M. Whitesides, *J. Am. Chem. Soc.*, **112**, 9670 (1990).

[14]   D. J. Cram and F. A. Abd Elhafetz, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

[15]   E. L. Eliel in Asymmetric Synthesis, Vol **2**, J. D. Morrison, ed, Academic Press, New York, 1983, p 125.

[16]   B. Reitstoyen, L. Kilaas, and T. Anthonsen, *Acta Chem. Scand.*, **B40**, 440 (1986).

[17]   H. G. Viehe and M. Reinstein, *Chem. Ber.*, **95**, 2557 (1962).

[18]   D. J. Nelson, R. DiFrancesco, and D. Petters, *J. Chem. Educ.*, **54**, 648 (1977).

[19]   Available from NIDA Drug Supply System, Research Technology Branch.