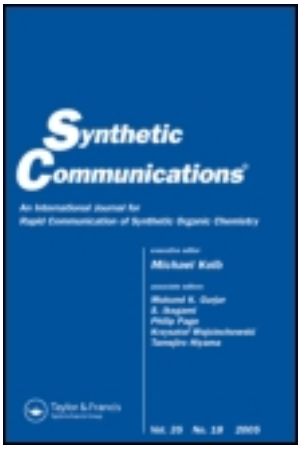

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Improved Syntheses of *N*-Desmethylcitalopram and *N*,*N*-Didesmethylcitalopram

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Abstract: An improved and efficient synthesis of *N*-desmethylcitalopram (**2**) and *N,N*-didesmethylcitalopram (**3**) is presented. The method involved *N*-demethylation of citalopram (**1**) using 1-chloroethyl chloroformate to give **2** in 87% yield. Synthesis of **3** was accomplished by alkylation of **8** with 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (**9**).

Keywords: citalopram, *N*-desmethylcitalopram, *N*,*N*-didesmethylcitalopram, *N*-demethylation

INTRODUCTION

Citalopram (CIT, **1**, Figure 1), a selective serotonin reuptake inhibitor (SSRI), is one of the most widely used antidepressants for the treatment of anxiety, obsessional, and control disorder.[1] CIT is metabolized mainly in the liver by cytochrome P450 (CYP2C19, CYP2D6, and CYP3A4 subtypes), and its most abundant active metabolites are *N*-desmethylcitalopram (DCIT, **2**) and *N*,*N*-didesmethylcitalopram (DDCIT, **3**).[2] To monitor citalopram and its metabolites in biological fluids by analytical methods (e.g., liquid chromatography and capillary electrophoresis), the authentic samples of DCIT and

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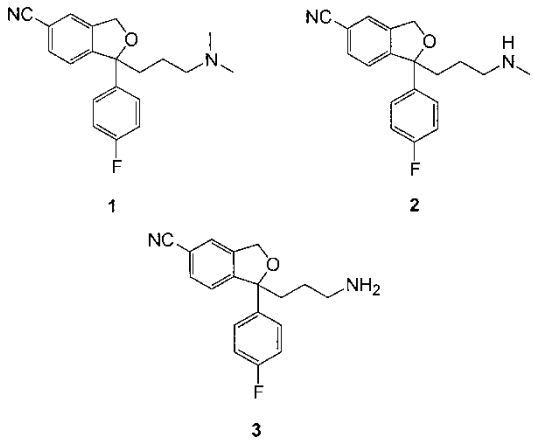


Figure 1. Structures of citalopram (**1**), *N*-desmethylcitalopram (**2**) and *N*,*N*-didesmethylcitalopram (**3**).

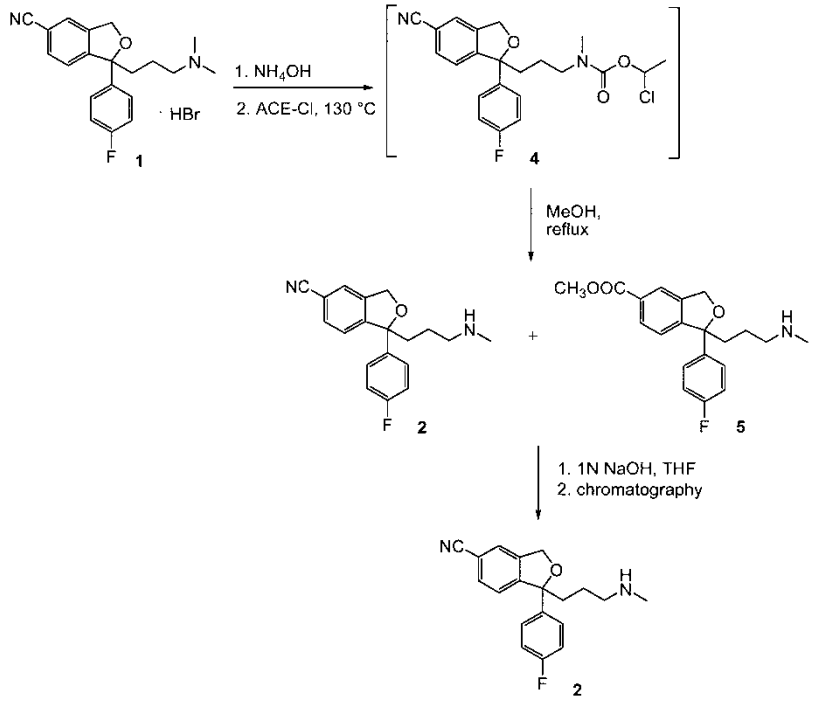
DDCIT were needed as standards. In 1977, Bigler and coworkers reported the first syntheses of DCIT and DDCIT.[3] DCIT was prepared by *N*-demethylation of citalopram using trichloroethyl chloroformate followed by zinc reduction in acetic acid. However, the yield of this demethylation was only 43%, and zinc dust is difficult to handle in a large-scale reaction and the subsequent workup process. In the case of DDCIT, experimental details of the key step, alkylation of 1-(4-fluorophenyl)-5-phthalancarbonitrile with 3-chloropropyl amine, were not given in the article. As a part of an ongoing research program, we needed to synthesize samples of DCIT and DDCIT. In this article, we report on an improved and efficient synthesis of DCIT and DDCIT.

RESULTS AND DISCUSSION

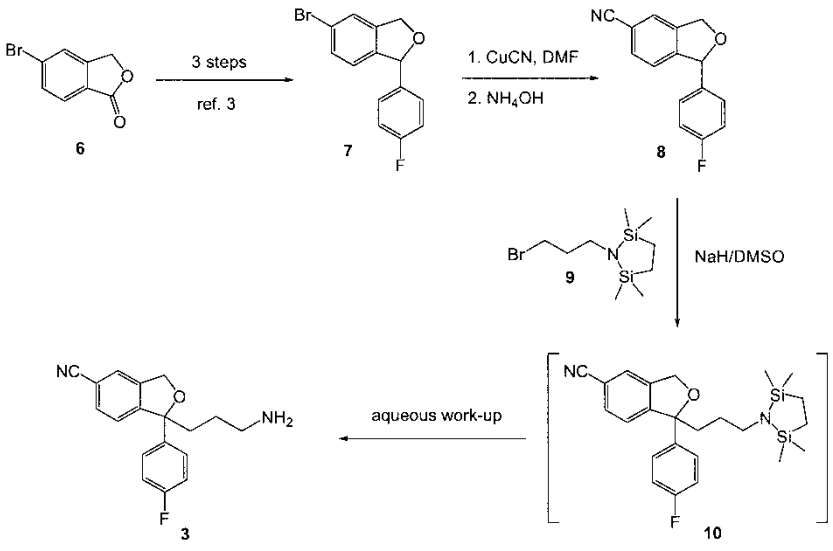
The *N*-demethylation of tertiary methylamines has been accomplished in several ways. These include reaction with cyanogen bromide (von Braun reaction)[4] or a substituted chloroformate[5] followed by cleavage of the resultant cyanamide or carbamate. Among those reported chlorofomates[6,7] 1-chloroethyl chloroformate (ACE-Cl) is one of the most selective and effective reagents for the *N*-demethylation reaction.[8] The application of ACE-Cl for *N*-demethylation of citalopram in 1,2-dichloroethane was first investigated. Citalopram (**1**) was treated with 4 equivalents of ACE-Cl in refluxing 1,2-dichloroethane for 24 h. Surprisingly, no *N*-demethylation product was observed based on ^{1}H NMR and MS spectral analyses of the crude product mixture. The starting material **1** was recovered in 81% yield. After extensive optimization, it was found that treatment of **1** with neat ACE-Cl (20 equivalents) at 130°C for 6 h generated carbamate **4**, which

was hydrolyzed without purification in boiling methanol to give crude *N*-desmethylcitalopram (**2**) (Scheme 1). This hydrolysis process also produced a small amount of methyl ester **5**, a by-product of an acid-catalyzed methanolysis of **2**. Column chromatography to separate **2** from **5** failed because of their similar polarities. Therefore, the ester **5** was converted to its carboxylate salt by treatment of the mixture with 1 N NaOH in THF. Subsequent chloromatography provided pure *N*-desmethylcitalopram (**2**) in 87% yield.

Synthesis of *N*,*N*-didesmethylcitalopram (**3**) was accomplished following the route outlined in Scheme 2. 1-(4-Fluorophenyl)-5-phthalancarbonitrile (**8**) was prepared in 58% yield from commercial 5-bromophthalide (**6**) following the literature report,[3] although a modification of the workup conditions was required for the last step. Thus, in our hands, 5-bromo-1-(4-fluorophenyl)phthalan (**7**) was treated with copper(I) cyanide in refluxing *N*,*N*-dimethylformamide for 6 h. Afterward, the reaction mixture was diluted with concentrated aqueous NH_4OH followed by bubbling the solution with a steam of air to remove copper(I). This avoided the use of highly toxic sodium cyanide in the workup. According to Bigler et a1.,[3] alkylation of **8** with 3-chloropropyl amine would produce *N*,*N*-didesmethylcitalopram (**3**). However, because the experimental detail and yield of this key step

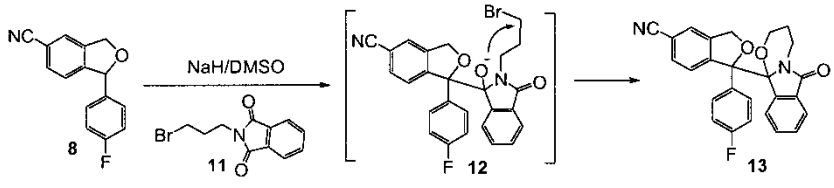


Scheme 1.



Scheme 2.

were not given in their paper, we decided to use a suitable *N*-protected 3-bromopropyl amine instead of the unprotected 3-chloropropyl amine because of the basic and nucleophilic nature of free NH_2 group. Double *N*-protected groups for primary amines including *N*,*N*-di(*t*-butoxycarbonyl), phthalimide, *N*,*N*-dibenyzl, and *N*,*N*-diallyl groups are well-documented in the literature.[9] However, these protecting groups meet with limitations or incompatibilities with regard to the alkylation procedure (e.g., phthalimide derivative[10] or the deprotection step (e.g., *N*,*N*-dibenyzl[11] and *N*,*N*-diallyl)[12]. Treatment of **8** with sodium methylsufinylmethide and *N*-(3-bromopropyl)phthalimide (**11**) gave **13** in 47% yield as the only isolated product.



It has been reported that the cyclic tetramethyldisilazane protecting group is stable in n-BuLi or lithium diisopropylamine (LDA) conditions required for alkylation.[13] The silyl protecting group can be easily removed using tetrabutylammonium fluoride (TBAF). Thus, 1-(4-fluoropheny1)-5-phthalancarbonitrile (**8**) was treated with sodium methylsufinylmethide, generated from sodium hydride and dimethylsulfoxide, followed by the addition

of 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (**9**). Surprisingly, the desired product **10** was not isolated after aqueous workup. Instead, *N*,*N*-didesmethylcitalopram (**3**), the desilylated product, was obtained pure in almost quantitative yield.

In summary, we report an improved and efficient synthesis of *N*-desmethylcitalopram (**2**) and *N*,*N*-didesmethylcitalopram (**3**). The method involved *N*-demethylation of citalopram (**1**) using 1-chloroethyl chloroformate to give **2** in 87% yield. *N*,*N*-Didesmethylcitalopram (**3**) was prepared in 57% yield from 5-bromophthalide.

EXPERIMENTAL

Melting points were determined on a Mel-Temp II capillary melting-point apparatus and are uncorrected. NMR (^{1}H and ^{13}C) spectra were obtained using a Bruker Avance DPX 300-MHZ NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. High resolution mass spectrum (HRMS) were recorded on a Waters Autospec Ultima mass spectrometer. Elemental analyses were done by Atlantic Microlab Inc., Norcross, GA. Analytical thin-layer chromatography (TLC) was carried out using EMD silica-gel 60 F_{254} TLC plates. Flash-column chromatography was done on a CombiFlash Companion system using Isco prepacked silica-gel columns. Reagents were normally obtained from Aldrich Chemical Company and used as received unless otherwise noted.

N-Desmethylcitalopram (2)

To a mixture of citalopram hydrobromide (0.55 g, 1.36 mmol) in EtOAc (50 mL), dilute aqueous NH_4OH (10 mL) was added. The EtOAc layer was separated, washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The resultant free base was dissolved in 1-chloroethyl chloroformate (2.96 mL, 2.72 mmol). The reaction mixture was heated 6 h at 130°C, cooled to room temperature, and then concentrated in vacuo. The residue was taken up in MeOH (15 mL) and refluxed for 5 h. After this time, the solvent was evaporated, and the residue was vacuum dried. The resultant crude product was dissolved in THF (5 mL), and 1 N NaOH (5 mL), was added to the solution. After stirring overnight, the reaction mixture was diluted with EtOAc (50 mL), washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (12 g of Isco silica-gel column) using 0 → 50% MeOH-CH_2Cl_2 afforded **2** (0.31 g, 87%) as an oil: ^{1}H NMR (300 MHz; $CDC1_3$) δ 1.25–1.55 (2H, m), 2.10–2.30 (2H, m), 2.39 (3H, s), 2.61 (2H, t, $J = 6.0$ Hz), 2.96 (1H, br s), 5.14 (1H, d, $J = 12$ Hz), 5.21 (1H, d, $J = 12$ Hz), 6.95–7.05 (2H, m), 7.36–7.48 (3H, m), 7.50 (1H, s), 7.66–7.75 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 23.7, 35.7, 38.8, 51.4, 71.3,

91.1, 111.7, 115.3 (d, $J_{C\text{-}F} = 21$ Hz), 118.6, 122.8, 125.2, 126.8 (d, $J_{C\text{-}F} = 8$ Hz), 131.9, 139.5 (d, $J_{C\text{-}F} = 3$ Hz), 140.3, 149.3, 162.0 (d, $J_{C\text{-}F} = 245$ Hz).

The free base was converted to the oxalate salt as a white solid: mp 139–141°C; ^{1}H NMR (300 MHz; CD_3OD) δ 1.40–1.65 (2H, m), 2.10–2.32 (2H, m), 2.54 (3H, s), 2.91 (2H, t, $J = 7.7$ Hz), 5.09 (1H, d, $J = 13.2$ Hz), 5.17 (1H, d, $J = 13.2$ Hz), 6.94–7.04 (2H, m), 7.43–7.65 (5H, m); Anal. calcd. for $C_{21}H_{21}FN_2O_5$: C, 62.99; H, 5.29; N, 7.00. Found: C, 62.65; H, 5.26; N, 6.96.

1-(4-Fluorophenyl)-5-phthalancarbonitrile (8)

A mixture of **7** (7.14 g, 24.0 mmol) and CuCN (2.58 g, 28.8 mmol) in DMF was refluxed 6 h under nitrogen. After being cooled to room temperature, the mixture was poured into concentrated aqueous NH_4OH (100 mL), and a strong steam of air was bubbled through the solution for 15 min. The resultant blue solution was extracted with benzene (3 × 50 mL). The combined benzene extracts were washed with NH_4OH (2 × 30 mL) and brine (3 × 30 mL), dried (Na_2SO_4, and concentrated in vacuo. Chromatography (80 g of Isco silica-gel column) using 0 → 20% EtOAc–hexanes afforded 2.44 g of the title compound. The recovered starting material **7** (3.80 g) was recycled to produce an additional product (2.13 g) that was combined with the previous sample to give **8** (4.57 g, 79% for two cycles) as a white solid: mp 95–97°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 5.20 (1H, d, $J = 12.3$ Hz), 5.34 (1H, dd, $J = 12.3$, 2.4 Hz), 6.16 (1H, s), 7.00–7.14 (3H, m), 7.20–7.32 (2H, m), 7.55 (1H, d, $J = 7.8$ Hz), 7.60 (1H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 72.5, 85.3, 111.8, 115.6 (d, $J_{C\text{-}F} = 21$ Hz), 118.7, 123.2, 125.1, 128.7 (d, $J_{C\text{-}F} = 8$ Hz), 131.8, 136.6 (d, $J_{C\text{-}F} = 3$ Hz), 140.4, 147.0, 162.7 (d, $J_{C\text{-}F} = 245$ Hz); EI HRMS calcd. for $C_{15}H_{10}FNO$ (M^+): 239.0746. Found: 239.0736.

N,*N*-Didesmethylcitalopram (3)

A mixture of NaH (60% in mineral oil, 0.62 g, 15.4 mmol) in DMSO (28 mL) was heated at 65°C under nitrogen for 20 min and then cooled to room temperature. A solution of **8** (3.35 g, 14.0 mmol) in DMSO (28 mL) was then added and stirred for 20 min. Afterward, 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (3.49 mL, 14.0 mmol) was added all at once, and the resultant reaction mixture was stirred at room temperature for 1 h. The mixture was then poured into ice water (100 mL), stirred 30 min, and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated in vacuo. The resultant residue was dissolved in 2N HCl (200 mL) and washed with Et_2O (3 × 50 mL). The aqueous layer was made basic using NH_4OH and extracted with EtOAc

(3 × 100 mL). The combined EtOAc extracts were washed with brine (3 × 50 mL) and dried (Na_2SO_4). Removal of solvent in vacuo afforded **3** (4.11 g, 99%) as an oil: ^{1}H NMR (300 MHz; $CDC1_3$) δ 1.12 (2H, br s), 1.21–1.54 (2H, m), 2.06–2.30 (2H, m), 2.68 (2H, t, $J = 7.1$ Hz), 5.14 (1H, d, $J = 13.5$ Hz), 5.21 (1H, d, $J = 13.5$ Hz), 6.94–7.06 (2H, m), 7.35–7.47 (3H, m), 7.51 (1H, s), 7.60 (1H, d, $J = 7.8$ Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 27.9, 38.3, 41.8, 70.9, 90.7, 111.2, 114.9 (d, $J_{C\text{-}F} = 21$ Hz), 118.4, 122.4, 124.9, 126.5 (d, $J_{C\text{-}F} = 8$ Hz), 131.5, 139.5 (d, $J_{C\text{-}F} = 3$ Hz), 140.0, 149.0, 161.6 (d, $J_{C\text{-}F} = 245$ Hz); ESI HRMS calcd. for $C_{18}H_{17}FN_2O$ $[M + H]^+$: 297.1403. Found: 297.1400.

The free base was converted to the oxalate salt as a white solid: mp 155–157°C; ^{1}H NMR (300 MHz; CD_3OD) δ 1.48–1.72 (2H, m), 2.18–2.40 (2H, m), 2.93 (2H, t, $J = 7.2$ Hz), 5.18 (1H, d, $J = 13.2$ Hz), 5.25 (1H, d, $J = 13.2$ Hz), 7.00–7.11 (2H, m), 7.51–7.72 (5H, m); Anal. calcd. for $C_{20}H_{19}FN_2O_5 \cdot 0.25H_2O$: C, 61.46; H, 5.03; N, 7.17. Found: C, 61.48; H, 5.05; N, 7.00.

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