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β-Naphthyl chlorothionoformate: an efficient, powerful and a new reagent for dealkylation tertiary amines

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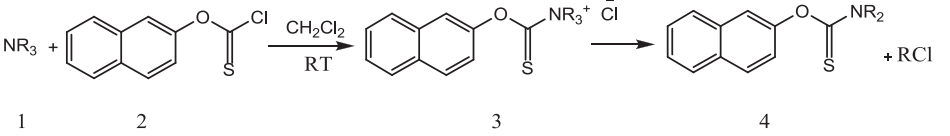
β-Naphthyl chlorothionoformate is introduced as a powerful dealkylating agent. This reagent reacts rapidly with tertiary amines at room temperature and produces their thiocarbamate derivatives, whose yields were from good to excellent. Rates of reactions and selectivity for alkyl group cleavage in amines were found to be superior or comparable to those previously reported with chloroformates.



1 2 3 4

Keywords: *β*-Naphthyl chlorothionoformate; dealkylation; tertiary amines; *β*-naphthyl thiocarbamate derivatives; synthesis

1. Introduction

N-Dealkylations, and more specifically debenzylations, are important in organic synthesis and structure determination. The previously reported methods for dealkylation of tertiary amines include the use of phenyl chlorothionoformate (*1*), thiophosgene and 1-chloroethyl chlorothionoformate (*2*), ethyl chloroformate (*3*), phenyl chloroformate (*4*), 1-chloroethyl chloroformate (*5*), 2,2,2-trichloroethyl chloroformate (*6*), vinyl chloroformate (*7*), propargyl chloroformate (*8*), electron deficient heteroaryl chlorides (*9*), 4-chlorophenyl chlorothionoformate, 2,4,6-tribromophenyl chlorothionoformate (*10*) and aryl chlorothionoformates (*11*).

In this paper, we introduce the use of *β*-naphthyl chlorothionoformate **2** for dealkylation of different tertiary amines. *β*-Naphthyl chlorothionoformate was even more reactive toward amines than previously studied chlorothionoformates and its dealkylation reactions were found to take place in higher yields and at room temperature.

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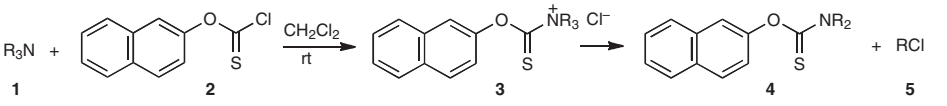
2. Result and discussion

The proposed route for dealkylation of tertiary amines with β-naphthyl chlorothionoformate involves the nucleophilic attack of the tertiary amines **1** on β-naphthyl chlorothionoformate **2** and subsequent decomposition of the salt **3** by chloride, forming the thiocarbamate **4** and an alkyl chloride **5** (Scheme 1).



Scheme 1. Dealkylation of tertiary amines.

The dealkylation of tertiary amines with β-naphthyl chlorothionoformate was more rapid than with the other reagents. By contrast, phenyl chlorothionoformate, 4-chlorothionoformate and 2,4,6-trichlorothionoformate converted *N*-methylpiperidine to the corresponding thicarbonates at room temperature in dichloromethane within 1 h, 40 min and 2 h, respectively. While the use of **2** at the same condition occurred cleanly in only 1 min. When triethylamine, *N*-methylpiperidine and *N*-methylmorpholine were treated with **2** in dichloromethane as a solvent, the de-ethylated (Entry 2) and the demethylated products (Entries 3 and 4) were obtained within 1 min in excellent amounts (Table 1).

When *N*,*N*-dimethylbenzylamine was treated with β-naphthyl chlorothionoformate in dichloromethane, only debenzylation was observed, as expected, in the quantitative yield and in only 1 min at room temperature (Entry 1). Exclusive debenzylation also occurred with $N-t$-butyl-*N*-methylbenzylamine and with *N*-allyl-*N*-methylbenzylamine (Entries 7 and 8). On the other hand, *N*-methylpyrrolidine and (-)-nicotine underwent primarily ring opening upon reaction with β-naphthyl chlorothionoformate (Entries 5 and 6).

Reaction of *N*,*N*-diethylaniline with β-naphthyl chlorothionoformate rather surprisingly dephenylation took place; this was proved by the isolation of a product that was shown to be identical to the thionocarbamate obtained from triethylamine (Entry 9), while *N*,*N*-dimethylcyclohexylamine resulted both in demethylation and in decyclohexylation (Entry 10).

3. Conclusion

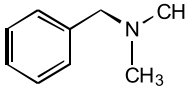
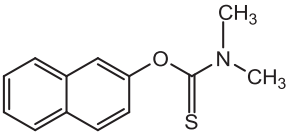
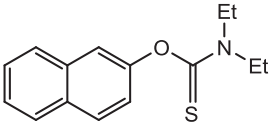
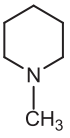
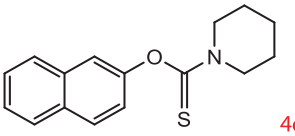
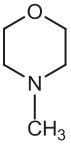
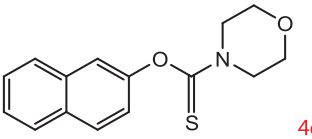
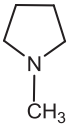
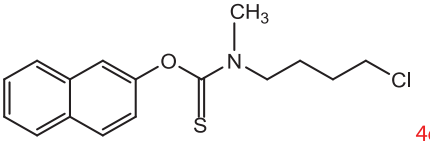
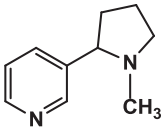
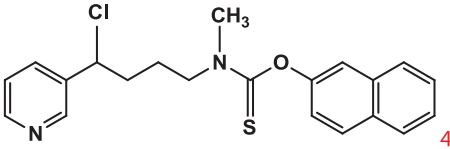
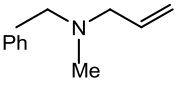
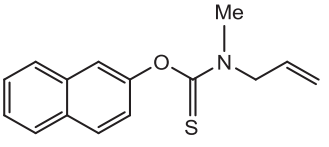
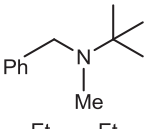
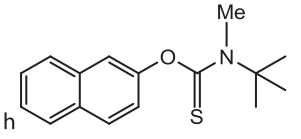
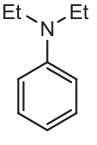
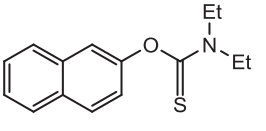
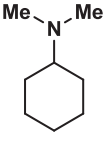
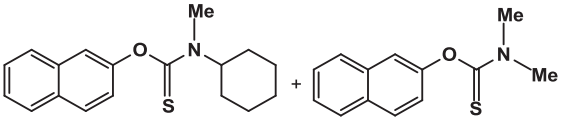
In conclusion, we have found a facile and efficient method for the dealkylation of tertiary amines by the reaction with β-naphthyl chlorothionoformate. The present procedure has many advantages such as short reaction times, mild conditions, high yields and easy operation procedures.

4. Experimental

4.1. *General*

^{1}H and ^{13}C NMR spectra were measured on a Bruker 300 spectrometer (at 300 MHz for ^{1}H spectra and 75 MHz for ^{13}C spectra) using TMS as an internal standard and $CDCl_3$ as solvent. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer instrument (KBr). Mass spectra were determined on an Agilent 6890-N-Network-GC system and melting points were recorded on an Electrothermal digital 8100 series apparatus.

Table 1. N-Dealkylation of tertiary amines with β-naphthyl chlorothionoformate.

Entry	Amines (**1**)	Time (min)	Products (**4**)	Yield[a] (%)
1		1	 4a	92
2	Et_3N	1	 4b	95
3		1	 4c	90
4		1	 4d	90
5		1	 4e	90
6		1	 4f	80
7		1	 4g	84
8		180	 4h	72
9		30	 4b	80
10		1	 4i + 4a	48 + 80

Note: [a]Isolated yields.

Organic solutions were dried with anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure to give the products. Substances purchased commercially were used without additional purification. The routine purifications of reagents and solvents were carried out by standard laboratory procedures.

4.2. *Typical procedure for the synthesis of β-naphthyl chlorothionoformate 2*

A solution of thiophosgene (3.2 ml, 0.042 mol) in dry dichloromethane (45 ml) was placed in a three-necked flask equipped with a water condenser, thermometer and a dropping funnel, in an ice-water bath. Then, a mixture of β-naphthol (5.4 ml, 0.024 mol) and 20% aqueous NaOH (35 ml) was added dropwise while stirring, and the resulting mixture was stirred at room temperature for an additional 1 h. After completion of the reaction, as monitored by TLC using petroleum ether/ethyl acetate (20/3), the organic layer was separated, washed with water (3×3 ml) and dried. After removal of the solvent, the resulting red crystals were recrystallized from *n*-hexane to yield pure product. Yellow crystals, mp 72 °C. FT-IR (KBr): 3058, 1626, 1508, 1356, 1232, 1011, 864, 757, 481, 230 cm^{-1}. ^{1}H NMR: $\delta = 7.28$–7.33 (1H, m); 7.53–7.63 (3H, m); 7.86–7.96 (3H, m). ^{13}C NMR: $\delta = 118.5$, 120.0, 126.6, 127.1, 128.0, 128.0, 130.1, 132.1, 133.6, 152.3, 185.9. EI-MS: m/z (%) = 224 $(M + 2)^+$, 222 (M^+), 187, 143, 127 (100), 94, 78. Found: M^+ 221.9906, $C_{11}H_7OSCl$ requires M^+ 221.9906.

4.3. *Typical procedure for dealkylation tertiary amines with β-naphthyl chlorothionoformate*

To the β-naphthyl chlorothionoformate **2** (0.1 g, 0.449 mmol) in dichloromethane (15 ml), tertiary amine (0.898 mmol) was added and the solution stirred at 25 °C for an appropriate time (Table 1) until the reaction was completed as monitored by petroleum ether/ethyl acetate (20/3). After completion of the reaction, the mixture was cooled to room temperature and the solvent was removed to obtain oily products that were crystallized from a mixture of *n*-hexane and ethanol to give pure products. The thiocarbamate products were converted into the secondary amine by treatment with dimethyl sulfate, followed by hydrolysis with water. All the products were characterized by mass spectrometry (MS) and spectral data (IR, ^{1}H NMR and ^{13}C NMR). The physical and spectral data for the thiocarbamates are given below:

4.3.1. *β-Naphthyl N,N-dimethylthiocarbamate* **(4a)**

Yellow crystals, mp 82 °C. FT-IR (KBr): 2928, 1629, 1532, 1508, 1393, 1293, 1244, 1146, 820, 747, 476 cm^{-1}. ^{1}H NMR: $\delta = 3.42$ (3H, s, CH_3), 3.51 (3H, s, CH_3), 7.25–7.29 (1H, m, Ar), 7.47–7.52 (3H, m, Ar), 7.83–7.89 (3H, m, Ar). ^{13}C NMR: $\delta = 38.8$, 43.3, 119.5, 122.5, 125.7, 126.5, 127.7, 127.9, 129.0, 129.4, 133.4, 153.1, 187.1. EI-MS: m/z (%) = 231 (M^+), 187, 143, 127, 104, 88 (100). Found: M^+ 231.0717, $C_{13}H_{13}NOS$ requires M^+ 231.0718.

4.3.2. *β-Naphthyl N,N-diethylthiocarbamate* **(4b)**

Orange crystals, mp 50 °C. FT-IR (KBr): 3055, 2976, 2933, 1629, 1599, 1509, 1428, 1314, 1209, 1165, 967, 855, 751, 472 cm^{-1}. ^{1}H NMR: $\delta = 1.36$ (3H, t, $J = 6$ Hz, CH_3), 1.38 (3H, t, $J = 6.0$ Hz, CH_3), 3.75 (2H, q, $J = 7.2$ Hz, CH_2), 3.95 (2H, q, $J = 7.2$ Hz, CH_2), 7.26–7.29 (1H, m, Ar), 7.42–7.55 (3H, m, Ar), 7.72–7.89 (3H, m, Ar). ^{13}C NMR: $\delta = 11.9$, 13.6, 44.3, 48.4, 119.5, 122.5, 125.7, 126.5, 127.7, 127.9, 129.7, 131.5, 133.7, 151.5, 186.9. EI-MS: m/z

(%) = 259 (M^+), 187, 143, 132, 127 (100), 116. Found: M^+ 259.1032, $C_{15}H_{17}NOS$ requires M^+ 259.1031.

4.3.3. *β-Naphthyl piperidine-1-thiocarboxylate* **(4c)**

Orange crystals, mp 98 °C. FT-IR (KBr): 2935, 2920, 2857, 1628, 1508, 1439, 1352, 1235, 1166, 1009, 803, 751, 473 cm^{-1}. ^1H NMR: $\delta = 1.77$ (6H, bs, $3CH_2$), 3.98 (2H, bs, CH_2N), 4.15 (2H, bs, CH_2N), 7.24–7.28 (1H, m, Ar), 7.46–7.51 (3H, m, Ar), 7.80–7.88 (3H, m, Ar). ^{13}C NMR: $\delta = 24.2, 25.3, 26.1, 47.5, 51.8, 119.4, 122.5, 125.7, 126.4, 127.7, 127.9, 128.9, 131.5, 133.7, 151.6, 186.3$. EI-MS: m/z (%) = 271 (M^+), 187, 143, 130, 128, 127 (100). Found: M^+ 271.1031, $C_{16}H_{17}NOS$ requires M^+ 271.1030.

4.3.4. *β-Naphthyl morpholine-4-thiocarboxylate* **(4d)**

Brown crystals, mp 131 °C. FT-IR (KBr): 2923, 1628, 1508, 1488, 1437, 1288, 1231, 1114, 1042, 817, 746, 473 cm^{-1}. ^1H NMR: $\delta = 3.80$–3.89 (4H, m, $2CH_2N$), 4.05 (2H, t, $J = 4.5$ Hz, CH_2O), 4.20 (2H, t, $J = 4.8$ Hz, CH_2O), 7.25 (1H, t, $J = 6.0$ Hz, Ar), 7.48–7.55 (3H, m, Ar), 7.81–7.89 (3H, m, Ar). ^{13}C NMR: $\delta = 46.9, 50.2, 66.2, 66.4, 119.5, 122.3, 125.8, 126.6, 127.7, 127.9, 129.0, 131.6, 133.7, 151.3, 187.3$. EI-MS: m/z (%) = 273 (M^+), 187, 146 (100), 143, 130, 127. Found: M^+ 273.0825, $C_{15}H_{15}NO_2S$ requires M^+ 273.0823.

4.3.5. *β-Naphthyl N-(4-chlorobutyl)-N-methylthiocarbamate* **(4e)**

Yellow oil. FT-IR (KBr): 2936, 1629, 1599, 1509, 1401, 1211, 856, 751, 473, 330 cm^{-1}. ^1H NMR: $\delta = 1.89$ (4H, d, $J = 3.9$ Hz, $2CH_2$), 3.34 (3H, s, CH_3), 3.45 (3H, s, CH_3), 3.62 (2H, q, $J = 6.3$ Hz, CH_2–Cl), 3.76–3.98 (2H, m, CH_2–N), 7.27 (1H, t, $J = 6.9$ Hz, Ar), 7.46–7.56 (3H, m, Ar), 7.82–7.90 (3H, m, Ar). ^{13}C NMR: $\delta = 23.9, 25.3, 29.6, 29.7, 36.8, 41.6, 44.4, 44.7, 50.8, 54.5, 119.5, 122.6, 125.8, 126.5, 127.7, 128.0, 129.0, 131.6, 133.7, 151.6, 187.8$. EI-MS: m/z (%) = 309 ($M^+ + 2$), 307 (M^+), 187, 182, 180, 166, 164, 143 (100), 127. Found: M^+ 307.0797, $C_{16}H_{18}ClNOS$ requires M^+ 307.0797.

4.3.6. *β-Naphthyl N-(4-chloro-4-(pyridin-3-yl)buty)l-N-methylthiocarbamate* **(4f)**

Yellow oil. FT-IR (KBr): 2925, 1717, 1628, 1599, 1509, 1402, 1240, 1162, 810, 748, 473 cm^{-1}. ^1H NMR: $\delta = 2.11$–2.29 (4H, m, $2CH_2$), 3.33 (3H, s, CH_3), 3.44 (3H, s, CH_3), 3.79–4.11 (2H, m, CH_2-N), 4.93–5.10 (1H, m, CH-Cl), 7.42–7.50 (3H, m, Ar), 7.52–7.66 (4H, m, Ar), 7.72–7.97 (6H, m, Ar), 8.51–8.59 (2H, m, Ar). ^{13}C NMR: $\delta = 24.0, 25.4, 29.7, 36.7, 36.9, 41.6, 50.7, 54.2, 59.9, 60.0, 119.5, 122.4, 124.0, 125.8, 126.6, 127.8, 129.1, 129.8, 131.5, 133.6, 134.9, 137.7, 147.8, 149.4, 151.4, 187.8$. EI-MS: m/z (%) = 372 $(M + 2)^+$, 370 (M^+), 245, 243, 229, 227, 187, 143 (100), 127. Found: M^+ 370.1030, $C_{21}H_{21}ClNOS$ requires M^+ 370.1032.

4.3.7. *β-Naphthyl N-allyl-N-methylthiocarbamate* **(4g)**

Yellow oil. FT-IR (KBr): 3056, 1600, 1509, 1398, 1211, 1164, 810, 751, 473 cm^{-1}. ^1H NMR: $\delta = 3.33$ (3H, s, CH_3), 3.47 (3H, s, CH_3), 3.38 (1H, d, $J = 5.4$ Hz, CH_2), 4.60 (1H, d, $J = 6$ Hz, CH_2), 5.25–5.38 (2H, m, CH_2), 5.92–5.97 (1H, m, CH), 7.26–7.32 (1H, m, Ar), 7.36–7.59 (3H, m, Ar), 7.83–7.90 (3H, m, Ar). ^{13}C NMR: $\delta = 36.2, 41.3, 53.9, 57.8, 117.8, 118.6, 119.5, 122.5, 125.8, 126.5, 127.8, 127.9, 129.0, 131.1, 131.5, 131.6, 133.7, 151.6, 187.9$. EI-MS: m/z (%) = 257 (M^+), 187, 143, 130, 127 (100), 114. Found: M^+ 257.0876, $C_{15}H_{15}NOS$ requires M^+ 257.0874.

4.3.8. *β-Naphthyl N-t-butyl-N-methylthiocarbamate* **(4h)**

Brown oil. FT-IR (KBr): 3055, 2925, 1758, 1600, 1509, 1459, 1381, 1241, 1213, 1162, 824, 748, 696, 474 cm^{-1}. ^1H NMR: $\delta = 1.39$ (9H, s, $3CH_3$), 3.59 (3H, s, CH_3), 7.10–7.27 (3H, m, Ar), 7.29–7.58 (3H, m, Ar), 7.76 (1H, q, $J = 8.7$ Hz, Ar). ^{13}C NMR: $\delta = 24.9$, 29.9, 30.3, 44.4, 54.0, 63.2, 118.4, 119.1, 121.0, 123.0, 126.6, 127.9, 129.1, 129.7, 131.3, 154.6, 187.1. EI-MS: m/z (%) = 273 (M^+), 187, 146, 143 (100), 130, 127. Found: M^+ 273.1188, $C_{16}H_{19}NOS$ requires M^+ 273.1187.

4.3.9. *β-Naphthyl N-cyclohexyl-N-methylthiocarbamate* **(4i)**

Yellow crystals, mp 107 °C. FT-IR (KBr): 2927, 2854, 1631, 1498, 1403, 1322, 1207, 1082, 969, 811, 751, 474 cm^{-1}. ^1H NMR: $\delta = 0.90$ (3H, q, $J = 4.2$ Hz), 1.29–1.72 (4H, m), 1.93 (4H, t, $J = 10.8$ Hz), 3.22 (s, 3H, CH_3), 3.38 (3H, s, CH_3), 7.27–7.30(1H, m, Ar), 7.45–7.52 (3H, m, Ar), 7.81–7.90 (3H, m, Ar). ^{13}C NMR: $\delta = 25.5$, 25.7, 29.4, 29.7, 30.6, 31.0; 58.2, 61.4, 119.5, 122.6, 125.7, 126.4, 127.7, 127.9, 128.8, 131.5, 133.7, 151.6, 187.3. EI-MS: m/z (%) = 299 (M^+), 187, 171, 155 (100), 143, 127. Found: M^+ 299.1343, $C_{18}H_{21}NOS$ requires M^+ 299.1344.

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