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Mild Deprotection of *tert*-Butyl Carbamates of NH-Heteroarenes under Basic Conditions

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Abstract: Aqueous methanolic potassium carbonate under reflux has been demonstrated to be a highly effective deprotective agent for the *tert*-butyl carbamates of indoles, indazoles, carbazole, thiazoloindole, and pyrrole. The method is a mild one and is particularly expeditious for NH-heteroarenes bearing electron-withdrawing groups.

Keywords: Aqueous K_2CO_3/MeOH, *N*-Boc-heteroarenes, deprotection, reflux

The proper choice of a protective group and its mild deprotection are of prime importance in the synthesis of polyfunctional molecules. Consequently, many books[1] and reviews[2] have been published on the extant methods of protection and deprotection of various functional groups. Moreover, updated reviews on this topic are also published periodically.[3] Of the common functionalities, amines, including those incorporated in nitrogen heteroarenes, are important in the fields of heterocycles and peptides. The *tert*-butoxycarbonyl group (Boc) is perhaps most widely used of the numerous protective agents used for amines, and it is also for aminoacids in peptide chemistry[4] because of the stability of the *tert*-butyl carbamates to basic and weakly acidic conditions. The amines are usually regenerated from their *N*-Boc derivatives by strong protic or Lewis acids or thermolysis.[1,5] The most common reagent is trifluoroacetic acid neat or in dichloromethane solution.

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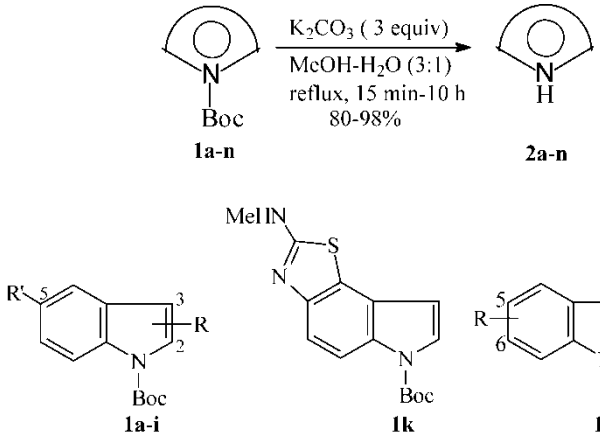
In recent years, methods have also been developed for the cleavage of *N*-Boc derivatives utilizing acidic solid catalysts such as silica gel (thermally,[6a] under low pressure[6b] or microwave irradiation,[6c] or doped with $Yb(OTf)_3$[6d]) and clays (kaolinitic[7a] or montmorillonite K10[7b]). Very recently, *n*-Bu_4NF,[8a,b] In/MeOH,[8c] CAN,[8d] LiBr,[8e] and so on have also been employed effectively for the cleavage of *N*-Boc derivatives.

The *N*-Boc group is generally found to be resistant to cleavage under basic conditions. In fact, two recent reports have shown that the *N*-Boc group was not cleaved by a mild base, viz. K_2CO_3 (CH_3CN/room temperature/24 h)[9a] and not even by a strong base, viz. NaO^{t}Bu ($PhCH_3$/40 °C/12 h).[9b] Nevertheless, the regeneration of amines from their *N*-Boc derivatives using basic reagents have been achieved in a few instances, for example, NaOMe/MeOH-THF for pyrroles,[10] $Mg(OMe)_2$/MeOH for lactams,[11] NaO^{t}Bu/moist THF or 2-Me-THF for both aromatic and aliphatic primary amines,[12] and lately by Cs_2CO_3/imidazole (CH_3CN/70 °C/4-24 h) mainly for the conversion of *N*,*N*-$(Boc)_2$-α-amino acids to their NH-Boc derivatives.[13] Of these, Cs_2CO_3/imidazole/CH_3CN was reported to cleave *N*-Boc-indole and *N*-Boc-oxindole (a lactam) to the respective parent heteroarene,[13] and NaOMe/MeOH was earlier reported to regenerate a few indoles from their *N*-Boc derivatives in isolated cases.[14] Thus, there does not appear to exist any generally applicable basic reagent, particularly a mild one, for the cleavage of *N*-Boc-heteroarenes to their parent NH-heteroarenes, in which we were interested.

In connecton with our recent work on the syntheses of a naturally occurring bisindolic enamide,[15] thiazoloindoles,[16] and indolyloxazoles,[17] we needed to develop a method for the cleavage of mainly the *N*-Boc-indoles to regenerate indoles using mildly basic conditions. As a result of our efforts, we have now been able to demonstrate that potassium carbonate (3 equiv) in methanol–water (3 : 1) under reflux efficiently deprotects the *N*-Boc derivatives of several indoles (**1a**–**i**), carbazole (**1j**), a thiazoloindole (**1k**), two nitroindazoles (**1l**,**m**), and 2-formylpyrrole (**1n**) to regenerate the parent heteroarenes (**2a**–**n**) in 80–98% isolated yields in 15 min–10 h. The reactions are presented in Scheme 1 and the results in Table 1.

An analysis of the results immediately unveiled a correlation between the electronic effects of the substituents on the heteroarenes and the reaction periods. Thus, the presence of an electron-withdrawing group (NO_2 in **1b**, **1l**, and **1m**; CHO in **1g** and **1n**) expedited the reactions (15–30 min), whereas for indole (**1a**), the presence of an electron-donating group (NHCSNHMe in **1f**; Br, OMe, NH_2, and Me in **1e**, **1d**, **1c**, and **1 h**, respectively) in the heteroarenes decelerated the reactions (2.5–5 h). In the case of 3-methylindole (**1i**), the reaction took an appreciably longer period (10 h), which is in conformity with the well-known reduced activity at C-2, compared to that at C-3, in the indole nucleus. Carbazole (**1j**) and the thiazoloindole (**1k**) required intermediate time periods for the completion of the reactions.

To ascertain the effectiveness of the reagent for the cleavage of the *N*-Boc derivatives of aromatic and aliphatic primary amines, the reagent was



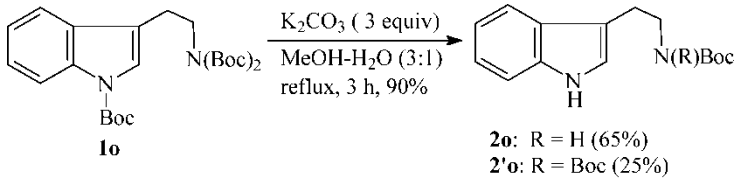
Scheme 1.

applied separately to the *N*-Boc derivatives of aniline, benzylamine, and β-phenylethylamine under similar conditions. In all three cases, the reagent proved to be abortive even after refluxing for 12 h, which pointed to the possible use of this reagent for the selective deprotection of *N*-Boc-heteroarenes in the presence of *N*-Boc aliphatic primary amines. Accordingly, *N*, *N*′,*N*′-$(Boc)_3$-tryptamine (**1o**)

Table 1. Deprotection of *N*-Boc-heteroarenes by K_2CO_3/aq. MeOH/reflux

Entry	*N*-Boc-heteroarenes (**1**)	Time	Yield (%)[a] of **2**
1	**a**: R = R′ = H	2.5 h	90
2	**b**: R = H; R′ = -NO_2	15 min	98
3	**c**: R = H; R′ = 5-NH_2	4.0 h	85
4	**d**: R = H; R′ = 5-OMe	3.5 h	82
5	**e**: R = H; R′ = -Br	3.0 h	87
6	**f**: R = H; R′ = NHCSNHMe	2.5 h	86
7	**g**: R = 3-CHO; R′ = H	20 min	95
8	**h**: R = 2-Me; R′ = H	5.0 h	92
9	**i**: R = 3-Me; R′ = H	10.0 h	85
10	**j**: Carbazole	1.0	91
11	**k**: A thiazoloindole	2.0 h	80
12	**l**: R = 5-NO_2	15 min	92
13	**m**: R = 6-NO_2	20 min	90
14	**n**: 2-Formylpyrrole	30 min	80
15	**o**: *N*, *N*′,*N*′-$(Boc)_3$-tryptamine	3.0 h	65 (**2o**)[b]; 25 (**2′o**)[b]

[a]Yields of isolated pure products.
[b]Separated by prep.TLC/silica gel/PE-EtOAc (4:1).



Scheme 2.

was subjected to similar basic conditions, and the reaction was complete in 3 h. Two products were formed, of which the major and the minor ones were identified as *N*′-Boc-tryptamine (**2o**; 65%) and *N*′, *N*′-$(Boc)_2$-tryptamine (**2′o**; 25%), respectively (Scheme 2). Thus, indolic *N*-deprotection took place in both the cases along with *N*′-mono-deprotection in the side chain in one case. Clearly, the reagent was a selective one, and more important, it appears to have the potential of being able to convert *N*, *N*-$(Boc)_2$-amines to *N*H-Boc-amines. However, we did not check the generality of this observation.

To our knowledge, this is the first general method of regeneration of several classes of NH-heteroarenes from their *N*-Boc derivatives using a mildly basic reagent. The method is environmentally benign, involves a simple workup, and employs an easy isolation procedure. Compared to the latest Cs_2CO_3/imidazole-mediated method,[13] the present method is distinctly superior on at least two counts. First, the use of a stoichiometric amount of imidazole creates waste, which renders the earlier method not eco-friendly; our present method avoids the use of any such waste-creating reagent. Second, the present method furnishes indole (from *N*-Boc-indole) more efficiently (90% yield in 2.5 h) than does the other method (82% yield in 24 h). Therefore, our method holds the promise of being widely used in the field of NH-heteroarenes, which is particularly expeditious for those NH-heteroarenes that bear electron-withdrawing groups at appropriate sites.

EXPERIMENTAL

Melting points (in Celsius) were recorded on a Toshniwal apparatus and are uncorrected. The IR spectra (nujol, unless stated otherwise) were recorded on a Nicolet Impact 410 FT-IR or a Perkin-Elmer-782 spectrophotometer, the ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra (including DEPT 135) on a Bruker DRX 500 NMR spectrometer, the LR EI-MS on a JEOL JMS-AX505HA, and ESI-MS (+ve; TOF) on a Micromass Q-Tofmicro mass spetrometer. The molecular formulae of all new compounds were determined either by HR EI-MS on a JEOL JMS-700 MStation or a Micromass Q-Tofmicro YA263 mass spectrometer or by elemental analyses. The analytical and preparative TLCs were carried out on silica gel G (Merck, India) plates. PE refers to petroleum ether, bp 60–80 °C.

Except for **1c**, **1f**, and **1k**, all other *N*-Boc-heteroarenes were prepared following the literature procedure.[18] compound **1c** was prepared from **1b** (by reduction with $NH_2NH_2 \cdot H_2O$, 10% Pd-C in refluxing methanol), **1f** from **1c** (by condensation with MeNCS), and **1 k** from **1f** (by cyclization using NBS-DBU).[16] Compounds **2a**–**e**, **2g**–**j**, **2l**–**n** were procured commercially. Because **1a**, **h**–**i**,[19a] **1d**,[19b] **1g**,[19c] **1j**,[19d] **2K**,[10] and **2o**[19e] are known compounds, their spectroscopic data are not presented here.

General Procedure for Deprotection

A solution of K_2CO_3 (0.414 g, 3 mmol) in MeOH-H_2O (3 : 1; ca. 15 mL) containing the *N*-Boc-heteroarene (1 mmol) was refluxed on a steam bath until the substrate was consumed (TLC). It was then diluted with water (10–15 mL), methanol was distilled off, and the solution cooled to room temperature. Either the resulting crystals were filtered (entries 2, 7, 10, 12, 13) or the products extracted (for the rest) with CH_2Cl_2 (3×20 mL). The pooled extracts were washed with water until free from alkali, dried (anhyd. Na_2SO_4), and filtered, and the filtrate was evaporated to residue. The resulting residue was purified by crystallization from PE-CH_2Cl_2 and identified either by direct comparison (mp, mixed mp, co-TLC) with an authentic sample (for known compounds) or by the usual spectroscopic and elemental analyses (for new products).

Data

1b: Mp 110–112 °C; IR: 1737, 1515, 1458, 1327, 1285, 1157, 1029, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.69 (9H, s), 6.70 (1H, d, $J = 3.5$ Hz), 7.73 (1H, d, $J = 3.5$ Hz), 8.19 (1H, dd, $J_1 = 9$ Hz, $J_2 = 2.5$ Hz), 8.25 (1H, d, $J = 9$ Hz), 8.47 (1H, d, $J = 2.5$ Hz); ^{13}C NMR: δ 28.5 (NCO_2CMe_3), 85.5 (NCO_2CMe_3), 108.2, 115.6, 117.6, 119.8, 129.2 (all Ar-CH), 130.7, 138.7, 144.1 (all Ar-C), 149.3 (carbamate CO); ESI-MS (+ve; TOF): m/z (%) 285 (M + Na; 14), 263 (M + H; 23), 206 (100), 161 (17); HR EI-MS: m/z 263.0261 ($M + H^+$). Calcd. for $C_{13}H_{15}N_2O_4$: 263.1028.

1c: Brown liquid; IR (neat): 3443, 3363, 1719, 1629, 1478, 1454, 1357, 1286, 1133, 1028, 859, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.64 (9H, s), 3.69 (2H, s), 6.38 (1H, d, $J = 3.5$ Hz), 6.71 (1H, dd, $J_1 = 8.5$ Hz, $J_2 = 2$ Hz), 6.83 (1H, d, $J = 2$ Hz), 7.49 (1H, s), 7.90 (1H, br); ^{13}C NMR: δ 28.6 (NCO_2CMe_3), 83.6 (NCO_2CMe_3), 106.6, 107.1, 114.1, 116.1, 126.7 (all Ar-CH), 129.7, 132.0, 142.0 (all Ar-C), 150.1 (carbamate CO); EI-MS: m/z (%) 232 (M^+; 33), 176 (100), 132 (92), 131 (28), 104 (10), 57 (43), 41 (15). Anal. calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.90; N, 12.07. Found: C, 67.20; H, 6.88; N, 12.08.

1d: Mp 74–76 °C (lit.[19b] mp 75–76 °C; no spectroscopic data were given); IR: 1732, 1613, 1586, 1533, 1447, 1281, 1122, 1023, 837, 804, 764, 724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.63 (9H, s), 3.79 (3H, s), 6.45 (1H, d, $J = 3.5$ Hz), 6.91 (1H, dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz), 6.99 (1H, d, $J = 2$ Hz), 7.54 (1H, s), 8.02 (1H, br); ^{13}C NMR: δ 28.6 ($NCO_2C\mathit{Me}_3$), 56.0 (OCH_3), 83.8 ($NCO_2\mathit{C}Me_3$), 103.9, 107.5, 113.4, 116.2, 126.9 (all Ar-CH), 130.3, 131.1, 156.3 (all Ar-C), 150.1 (carbamate CO); EI-MS: m/z (%) 247 (M^+; 34), 191 (100), 147 (47), 132 (38), 57 (48), 41 (12); HR EI-MS: m/z 247.1211 (M^+). Calcd. for $C_{14}H_{17}NO_3$: 247.1209.

1e: Mp 58–60 °C; IR: 1739, 1573, 1533, 1275, 1248, 1162, 1082, 1023, 764 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66 (9H, s), 6.49 (1H, d, $J = 3.5$ Hz), 7.38 (1H, dd, $J_1 = 9$ Hz, $J_2 = 1.5$ Hz), 7.57 (1H, d, $J = 3.5$ Hz), 7.67 (1H, d, $J = 1.5$ Hz), 8.01 (1H, br d, $J = 8$ Hz); ^{13}C NMR: δ 28.5 ($NCO_2C\mathit{Me}_3$), 84.5 ($NCO_2\mathit{C}Me_3$), 106.8, 116.9, 123.9, 127.4 ($\times 2$) (all Ar-CH), 116.3, 132.6, 134.3 (all Ar-C), 149.8 (carbamate CO); EI-MS: m/z (%) 297 ($M + 2$; 18), 295 (M^+; 18), 241 (40), 239 (40), 224 (10), 222 (10), 197 (63), 195 (66), 116 (27), 115 (27), 57 (100), 41 (53); HR EI-MS: m/z 295.0197 (M^+). Calcd. for $C_{13}H_{14}NO_2^{79}Br$: 295.0208.

1f: Mp 172–174 °C (dec.); IR: 3363, 3169, 1719, 1547, 1469, 1327, 1299, 1155, 1049, 764 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.61 (9H, s), 2.89 (3H, d, $J = 4.5$ Hz), 6.68 (1H, d, $J = 3.5$ Hz), 7.19 (1H, d, $J = 8.5$ Hz), 7.49 (1H, br s), 7.56 (1H, s), 7.65 (1H, d, $J = 3.5$ Hz), 7.96 (1H, d, $J = 8.5$ Hz), 9.50 (1H, br s); ^{13}C NMR: δ 27.6 ($NCO_2C\mathit{Me}_3$), 31.3 (N-CH_3), 83.8 ($NCO_2\mathit{C}Me_3$), 107.5, 114.7, 116.7, 121.5, 126.6 (all Ar-CH), 130.4, 131.9, 133.7 (all Ar-C), 149.0 (carbamate CO), 181.3 (C═S); EI-MS: m/z (%) 305 (M^+; 100), 249 (45), 216 (29), 215 (28), 205 (26), 193 (48), 176 (69), 132 (76), 131 (32), 74 (25), 57 (86), 41 (25). Anal. calcd. for $C_{15}H_{19}N_3O_2S$: C, 59.01; H, 6.23; N, 13.77. Found: C, 59.07; H, 6.21; N, 13.80.

1k: Mp 180–182 °C (dec.); IR (KBr): 3232, 1733, 1621, 1562, 1426, 1367, 1278, 1154, 763 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.68 (9H, s), 3.12 (3H, d, $J = 5.5$ Hz), 5.92 (1H, br s), 6.50 (1H, d, $J = 3.5$ Hz), 7.51 (1H, d, $J = 8.5$ Hz), 7. 64 (1H, d, $J = 3.5$ Hz), 8.10 (1H, d, $J = 8.5$ Hz); ^{13}C NMR: δ 27.2 ($NCO_2C\mathit{Me}_3$), 31.3 (N-CH_3), 83.3 ($NCO_2\mathit{C}Me_3$), 104.7, 112.8, 114.9, 126.0 (all Ar-CH), 120.5, 123.4, 130.3, 148.1, 166.9 (all Ar-C), 149.1 (carbamate CO); EI-MS: m/z (%) 303 (M^+; 28), 247 (100), 203 (35), 202 (17), 175 (13), 174 (25), 57 (26), 41 (11). Anal. calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.40; H, 5.61; N, 13.86. Found: C, 59.33; H, 5.60; N, 13.89.

1l: Mp 128–130 °C; IR: 1765, 1613, 1527, 1341, 1295, 1149, 1029, 830 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.45 (9H, s), 7.98 (1H, d, $J = 9$ Hz), 8.17 (1H, dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz), 8.40 (1H, s), 8.60 (1H, d, $J = 2$ Hz); ^{13}C NMR: δ 28.4 ($NCO_2C\mathit{Me}_3$), 86.5 ($NCO_2\mathit{C}Me_3$), 115.6, 119.5, 124.5, 141.8 (all

Ar-CH), 126.2, 142.1, 144.5 (all Ar-C), 148.7 (carbamate CO); ESI-MS (+ve; TOF): m/z (%) 286 (M + Na; 100), 264 (M + H; 3), 230 (20), 208 (36), 179 (22), 123 (75). Anal. calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.94; N, 15.97. Found: C, 54.72; H, 4.95; N, 15.95.

1m: Mp 134–136 °C; IR: 1738, 1534, 1410, 1300, 1372, 1253, 1160, 1082, 1025, 890, 784 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.76 (9H, s), 7.88 (1H, dd, $J_1 = 9$ Hz, $J_2 = 1$ Hz), 8.20 (1H, dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz), 8.30 (1H, d, $J = 1$ Hz), 9.12 (1H, s); ^{13}C NMR: δ 28.4 (NCO_2CMe_3), 86.8 (NCO_2CMe_3), 111.5, 119.0, 122.1, 139.2 (all Ar-CH), 129.4, 139.2, 148.5 (all Ar-C), 148.7 (carbamate CO); ESI-MS (+ve; TOF): m/z (%) 286 (M + Na; 86), 264 (M + H; 3), 230 (13), 208 (100), 164 (48). Anal. calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.94; N, 15.97. Found: C, 54.70; H, 4.93; N, 15.95.

1n: Mp 50–52 °C; IR: 1750, 1655, 1541, 1249, 1124, 1024, 844, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64 (9H, s), 6.28 (1H, t, $J = 3$ Hz), 7.18–7.19 and 7.43–7.44 (1H, m each), 10.32 (1H, s); ^{13}C NMR: δ 28.3 (NCO_2CMe_3), 86.1 (NCO_2CMe_3), 112.0, 121.5, 127.1 (all Ar-CH), 135.1 (Ar-C), 148.7 (carbamate CO), 182.7 (CHO); ESI-MS (+ve; TOF): m/z (%) 218 (M + Na; 47), 196 (M + H; 2); 162 (73), 140 (100), 96 (55), 68 (19); HR EI-MS: m/z 196.0724 ($M + H^+$). Calcd. for $C_{10}H_{14}NO_3$: 196.0974.

1o: Mp 76–78 °C; IR: 1732, 1699, 1367, 1255, 1082, 864, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (18H, s), 1.65 (9H, s), 2.97 and 3.86 (2H, t each, $J = 7.5$ Hz), 7.24 and 7.30 (1H, t each, $J = 7.5$ Hz), 7.39 (1H, s), 7.61 (1H, d, $J = 7.5$ Hz), 8.11 (1H, ill-split d); ^{13}C NMR: δ 25.0 (CH_2), 28.4 ($2 \times NCO_2CMe_3$), 28.6 ($1 \times NCO_2CMe_3$), 46.7 (CH_2), 82.6 ($2 \times NCO_2CMe_3$), 83.7 ($1 \times NCO_2CMe_3$), 115.6, 119.4, 122.8, 123.6, 124.7 (all Ar-CH), 118.0, 131.0, 135.9 (all Ar-C), 150.1 ($1 \times$ carbamate CO), 152.9 ($2 \times$ carbamate CO); EI-MS: m/z (%) 460 (M^+; 23), 404 (5), 360 (6), 260 (23), 248 (36), 204 (76), 187 (53), 143 (87), 130 (70), 57 (100), 41 (24); HR EI-MS: m/z 460.2567 (M^+). Calcd. for $C_{25}H_{36}N_2O_6$: 460.2574.

2f: Mp 158–160 °C; IR: 3356, 3224, 3177, 1560, 1520, 1314, 1261, 1043, 758, 724 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.86 (3H, d, $J = 4$ Hz), 6.40 (1H, s), 6.90 (1H, d, $J = 8$ Hz), 7.21 (1H, br s), 7.34 (1H, s), 7. 35 (1H, d, $J = 8$ Hz), 7.37 (1H, s), 9.34 (1H, br s), 11.09 (1H, s); ^{13}C NMR: δ 32.3 (N-CH_3), 102.2, 112.5, 117.7, 120.5, 127.0 (all Ar-CH), 128.6, 130.5, 134.9, 182.2 (all Ar-C); EI-MS: m/z (%) 205 (M^+; 100), 174 (16), 172 (29), 171 (32), 157 (15), 156 (15), 132 (87), 116 (15), 104 (23), 89 (13), 74 (13); HR EI-MS: m/z 205.0674 (M^+). Calcd. for $C_{10}H_{11}N_3S$: 205.0673.

2′o: Mp 122–124 °C; IR: 3317, 1732, 1255, 1142, 864, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (18H, s), 3.04 and 3.87 (2H, t each, $J = 7$ Hz), 6.99 (1H, s), 7.11 and 7.17 (1H, t each, $J = 7.5$ Hz), 7.34 and 7.67 (1H, d each, $J = 8$ Hz),

8.14 (1H, s); ^{13}C NMR: δ 25.3 (CH_2), 28.4 ($NCO_2C\mathit{Me}_3$), 47.5 (CH_2), 82.5 ($NCO_2\mathit{C}Me_3$), 111.5, 119.3, 119.7, 122.3, 122.5 (all Ar-CH), 113.4, 128.0, 136.6 (all Ar-C), 152.9 (carbamate CO); EI-MS: m/z (%) 360 (M^+; 13), 260 (23), 248 (36), 204 (27), 203 (10), 187 (10), 159 (11), 143 (74), 130 (100), 57 (26); HR EI-MS: m/z 360.2035 (M^+). Calcd. for $C_{20}H_{28}N_2O_4$: 360.2049.

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