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Very efficient one-pot conversion of *N*-aminophthalimide derivatives into the corresponding *N*-amino-di-*tert*-butyl imidodicarbonates

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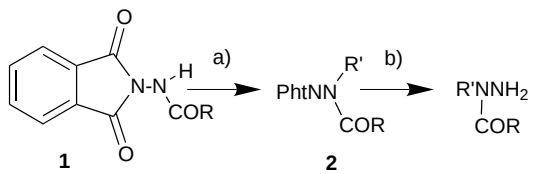
Abstract—The phthaloyl group can be efficiently converted in very mild conditions into bis-*tert*-butyloxycarbonyl group using $MeNH_2$, then Boc_2O/DMAP, in a one-flask protocol. © 2002 Elsevier Science Ltd. All rights reserved.

The phthalimide group has provided the classical means for the direct introduction of masked amino function via the Gabriel protocol[1] as well as for the protection of amino groups.[2,3] Recently, we demonstrated that phthalimide derivatives can also be efficiently used for the synthesis of *N*-alkylated hydrazine derivatives.[4] As a result, we showed that *N*-acyl and *N*-protected aminophthalimides can be considered as hydrazines bearing three electron-withdrawing groups including two incorporated into the phthaloyl moiety. This structural arrangement enabled us to use, for the first time, these hydrazine derivatives as acidic partners in the Mitsunobu reaction. This protocol was highly efficient to obtain in two steps *N*-alkylated hydrazides or carbazates[4a] and enantiomerically pure α-hydrazinoacid derivatives[4b] (Scheme 1).

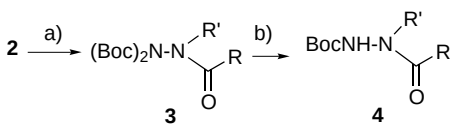
We showed that the presence of the phthaloyl group was essential for the success of this reaction by contributing to the increase in acidity of the sole proton and concomitantly to reduce steric hindrance. Unfortunately, as other authors reported,[5] we were confronted with the difficulty of finding general and mild conditions to remove the phthaloyl group. In some cases, this drawback depreciated this new strategy of synthesis of hydrazine derivatives. *N*-*tert*-Butyloxycarbonyl (Boc) is among the most utilized protecting groups and plays a critical role in amino acid and peptide chemistry since it is easily removed and is compatible with solid-phase synthesis.[2,3,6] In order to find mild and efficient conditions to remove the phthaloyl group and concomitantly to obtain Boc protection of our hydrazine derivatives, we were interested in developing a strategy which would enable us to transform a phthaloyl into a Boc group.



Scheme 1. (a) R′OH, DEAD, PPh_3, THF; (b) CH_3NHNH_2, THF.

Herein, we describe a one-flask protocol for the conversion of phthaloyl-hydrazides or -carbazates **2** into the corresponding *N*,*N*-bis-*tert*-butyloxycarbonyl-hydrazides or -carbazates **3** in high yields by treatment with methylamine followed by the action of $(Boc)_2O$/DMAP (Scheme 2).

In preliminary studies, we showed that compounds **2** cannot be dephthaloylated by using the $MeNH_2$, which



Scheme 2. (a) $MeNH_2$, THF, rt, 3 h; evaporation; $(Boc)_2O$, DMAP cat., THF, rt (b) $Mg(ClO_4)_2$ cat., CH_3CN.

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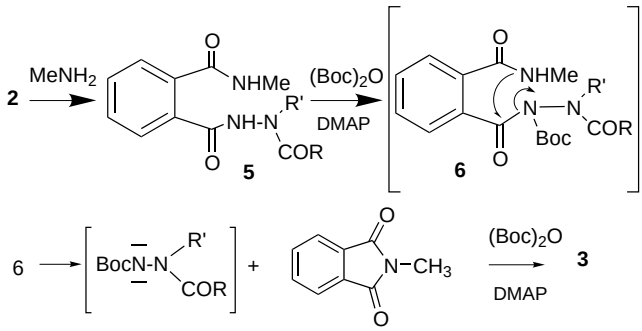
was described to allow the dephthaloylation of some protected amines.[7] Applied to compounds **2**, these conditions led in fact to the formation of compounds **5** resulting from an opening of the phthaloyl ring instead of the corresponding deprotected hydrazides or carbazates. We reasoned that the fixation of an electron-withdrawing group onto the acidic nitrogen atom of the hydrazide function could allow the dephthaloylation by favoring the split of the CO–N bond of the hydrazide group of **5**. This strategy has been previously reported in the literature since amides can be activated to hydrolysis by prior conversion to the *N*-Boc imide derivatives.[8] As a result, we showed that the removal of the phthaloyl group of **2** can be achieved very efficiently by using $(Boc)_2O$ in the presence of a catalytic amount of DMAP. These last conditions led in fact to the direct formation of the corresponding 1,1-di-(*tert*-butyloxycarbonyl) hydrazides or carbazates **3**. Systematic assays performed on compound **2** $R=OCH_2Ph$, $R'=CH_2Ph$ demonstrated that the reaction was better achieved using 3 equiv. of $(Boc)_2O$, the use of 1 equiv. of reagent leading to the formation of a mixture of compounds **3** and **4** (with 25 and 55% yields, respectively). To improve our technique we investigated performing the conversion of phthaloyl hydrazides or carbazates **2** into the corresponding compounds **3** in a one-flask protocol which could potentially find use in the combinatorial synthesis of Boc-protected hydrazides or carbazates. A general procedure is as follows: to a solution of compound **2** (3 mmol) in THF (20 mL) was added at room temperature a solution of methylamine (4.5 mmol, 2 mol L^{-1} in MeOH). The mixture was stirred at room temperature until completion (monitored by tlc). The solvent and the excess of amine were removed in vacuo. To the white solid those obtained dissolved in THF (20 mL) was added $(Boc)_2O$ (9 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature until completion (monitored by tlc); the solvent was removed in vacuo and the residue is separated by column chromatography.[9] The results of these transformations are shown in Table 1.[10] Regardless of the nature of R or R′, the yields in compounds **3** are very good. It is important to note that this procedure is still efficient when $R'=CH(CH_3)COOEt$ and could represent a new method for the preparation of orthogonal N^{α},N^{β}-triprotected α-hydrazinoesters. The production of compounds **3** can be explained by the reaction mechanism given in Scheme 3. As described above the action of the methylamine gives the corresponding compound **5** which can be isolated if necessary. Then, the mechanism predicts that $(Boc)_2O$ would selectively protect the nitrogen of the hydrazide group of compounds **5**, leaving unprotected those of the amide group which should react with the carbonyl group of the phenyl hydrazide and lead to the split of the C–N bond. To test this hypothesis, pyrolidine, a secondary amine was used instead of the methylamine which allowed us to isolate the pyrolidino analogue of compound **6** which was characterized by ^1H and ^{13}C NMR. Furthermore, the isolation and the identification of methylphthalimide as a by-product of the reaction is also in agreement with the proposed reaction mechanism.

Table 1. Di- and mono-*tert*-butyloxycarbonyl hydrazine derivatives produced via Scheme 2

2		**3** % yield[a]	**4** % yield[b]
R	R′		
CH_3	CH_3	90	85
CH_3	CH_2Ph	94	81
Ph	CH_3	75	86
Ph	CH_2Ph	80	80
^{t}BuO	CH_3	82	96
^{t}BuO	CH_2Ph	91	84
OCH_2Ph	CH_3	76	98
OCH_2Ph	CH_2Ph	80	96
OCH_2Ph	$CH(CH_3)COOEt$	90	80

[a] Yields of compounds **3** calculated from **2**.
[b] Yields of compounds **4** calculated from **3**.



Scheme 3. Proposed reaction mechanism for the production of compounds **3**.

The introduction of the second Boc group would be the result of the reaction of second equivalent of $(Boc)_2O$. Finally, using a described procedure,[11] di-*tert*-butyloxycarbonyl groups underwent mild and selective monodeprotection by action of a catalytic amount of $Mg(ClO_4)_2$ in CH_3CN to yield compounds **4** (Scheme 2, Table 1). In summary, it has been shown that *N*-aminophthalimide derivatives can be efficiently converted into the corresponding *N*-amino-di-*tert*-butylimidodicarbonates using a three-stage one-flask protocol in very mild conditions. A selective removal of one Boc group on the diprotected nitrogen leads to the formation of *N*-*tert*-butyloxycarbonyl hydrazine derivatives in good yields. We showed on one example that these procedures could also be used for the preparation of orthogonal N^{α},N^{β}-diprotected α-hydrazinoesters. Extension of this method to other α-hydrazinoacid and peptide derivatives is currently under investigation.

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9. Merck silica gel 60 was used for all chromatographic separations. The separation of compounds **3** was achieved by using a column chromatography ($\varnothing = 3$ cm) and a mixture EtOAc/hexane as eluant. As an indication: R_f (methylphthalimide) = 0.45 with hexane/EtOAc 4/1.
10. ^{1}H and ^{13}C NMR spectra of all new compounds: **3** R = Ph, R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ 7.32–7.10 (m, 5H), 3.06 (s, 3H), 1.36 and 1.25 (2s, 18H); ^{13}C NMR: δ 172.7, 149.9, 134.8, 130.7, 128.2, 126.8, 84.6, 35.5, 28.1. **3** R = Ph, R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.57–7.22 (m, 10H), 4.89 (s, 2H), 1.43 and 1.29 (2s, 18H); ^{13}C NMR: δ 172.8, 135.2, 135.1, 131.1, 130.7, 128.8, 128.6, 128.3, 128.2, 84.7, 52.6, 28.2. **3** R = CH_3 R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 3H), 1.93 (s, 3H), 1.50 (s, 18H); ^{13}C NMR: δ 172.4, 150.0, 84.9, 34.9, 28.3, 20.2. **3** R = CH_3 R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.27–7.16 (m, 5H), 4.61 (s, 2H), 1.91 (s, 3H), 1.27 (s, 18H); ^{13}C NMR: δ 172.6, 150.0, 135.3, 130.7, 128.7, 128.2, 54.6, 51.4, 28.1, 20.5. **3** R = OCH_2Ph, R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ ^{13}C NMR: δ 155.3, 150.2, 136.4, 128.8, 128.6, 128.3, 84.1, 68.4 and 68.1, 37.4 and 36.7, 28.2. **3** R = OCH_2Ph, R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.45–7.24 (m, 10H), 5.20 (s, 2H), 4.67 (s, 2H), 1.36, 1.29 (2s, 18H); ^{13}C NMR: δ 155.5, 150.3, 136.3, 135.4, 130.6, 130.2, 128.8, 128.7, 128.6, 128.4, 84.0, 68.7, 68.3, 54.9, 53.9, 28.1. **3** R = OCH_2Ph, R′ = $CH(CH_3)$COOEt: ^{1}H NMR ($CDCl_3$): δ 7.38–7.26 (m, 5H), 5.29–5.17 (m, 2H), 4.58 (q, $J = 7$ Hz, 1H), 4.20 (t, $J = 7$ Hz, 3H), 1.51, 1.47, 1.45, 1.40 (4s, 18H), 1.36 (d, $J = 7$ Hz, 3H), 1.26 (t, $J = 7$ Hz, 3H). ^{13}C NMR: δ 155.5, 150.3, 136.3, 135.4, 130.6, 130.2, 128.8, 128.7, 128.6, 128.4, 84.0, 68.7, 68.3, 54.9, 53.9, 28.1.**4** R = Ph, R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ 7.44–7.22 (m, 5H), 3.23 (s, 3H), 1.35 (s, 9H); ^{13}C NMR: δ 134.9, 130.6, 128.3, 127.6, 82.0, 28.4. **4** R = Ph, R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.62–7.22 (m, 10H), 6.75 (s, 1H), 6.61–4.07 (m, 2H), 1.31 (s, 9H). ^{13}C NMR: δ 154.4, 136.2, 135.3, 130.5, 129.1, 129.0, 128.3, 128.0, 127.7, 82.0, 28.6. **4** R = CH_3, R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ 7.71 (s, 1H), 3.05 (s, 3H), 2.01 (s, 3H), 1.12 (s, 9H).^{13}C NMR: δ 174.3, 154.7, 82.0, 36.0, 28.5, 20.7. **4** R = CH_3, R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.34–7.12 (m, 5H), 5.36–4.27 (m, 2H), 2.02 (s, 3H), 1.37 (s, 9H). ^{13}C NMR: δ 174.0, 154.6, 136.2, 129.3, 129.1, 128.1, 81.9, 50.8, 28.4, 20.1 **4** R = OCH_2Ph, R′ = CH_3: ^{1}H NMR ($CDCl_3$): δ 7.39–7.24 (m, 5H), 5.14 (s, 2H), 3.17 (s, 3H), 1.42 (s, 9H). ^{13}C NMR: δ 156.8, 136.5, 128.8, 128.5, 128.3, 81.8, 68.2, 38.3, 28.6. **4** R = OCH_2Ph, R′ = CH_2Ph: ^{1}H NMR ($CDCl_3$): δ 7.57–7.06 (m, 10H), 6.68–6.17 (m, 1H), 5.23 (s, 2H), 4.75 (s, 2H), 1.44 (s, 9H); ^{13}C NMR: δ 156.7, 136.9, 136.4, 129.2, 129.0, 128.6, 128.3, 128.2, 128.1, 82.0, 68.6, 54.0, 28.5. **4** R = OCH_2Ph, R′ = $CH(CH_3)$COOEt: ^{1}H NMR ($CDCl_3$): δ 7.39–7.26 (m, 5H), 6.69–6.52 (m, 1H), 5.22 (pd, 1H), 5.10 (pd, 1H), 5.05–4.95, 4.85–4.73 (2m, 1H), 4.23–4.03 (m, 2H), 1.47 (d, $J = 7$ Hz, 3H), 1.39, 1.35 (2s, 9H), 1.29–1.14 (m, 3H). ^{13}C NMR: δ 172.6, 156.4, 155.5, 136.1, 128.8, 128.5, 128.1, 81.6, 68.7, 61.8, 28.4, 14.5. For the other compounds, see Ref. 12.
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