Pergamon

Tetrahedron Letters 41 (2000) 2343–2346

TETRAHEDRON LETTERS

# *tert*-Butoxycarbamate group: a useful protecting group for the synthesis of orthogonally protected 'tropane-like' scaffolds

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Received 20 December 1999; accepted 27 January 2000

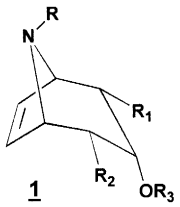
**Abstract**

The first synthesis of *N*-Boc-protected tropanes by a [4+3] cycloaddition reaction is described. The Boc group has been cleanly removed demonstrating that this group would be very useful for the synthesis of 'tropane-like' scaffolds for combinatorial chemistry. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* [4+3] cycloaddition; combinatorial chemistry; protecting groups; tropanes.

Combinatorial chemistry started only a decade ago and is now an emerging field.[1] For instance, compound libraries are important tools for the discovery and optimisation of new leads in medicinal chemistry. For the preparation of libraries with a large molecular diversity it is necessary not only to efficiently control reactivity on support but also to develop novel scaffolds.

As part of our research program in this area, we selected new 'tropane-like' scaffolds[2] of general structure **1** (Scheme 1).




**1**

Scheme 1.

This choice is based upon two factors: first, the molecules belonging to this family are known to exhibit potent biological properties,[3] and secondly, they display a tridimensional rigid skeleton which would be of great interest for the building of libraries.

The framework of our target molecules can be built by a [4+3] cycloaddition reaction[4] between dibromoketones and *N*-alkoxycarbonylpyrroles in the presence of diethylzinc,[5] but this reaction is

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*PII:* S0040-4039(00)00198-2

usually performed on *N*-methoxycarbonylpyrroles. However, the conditions reported for the deprotection of *N*-ethoxycarbonyl-protected tropanes or closely related compounds are drastic; either TMSI[2a] or concentrated HCl at high temperatures[6] have been used. Therefore, this protecting group cannot be easily introduced into a pool of orthogonal-protecting groups and is unsuitable for routine use in combinatorial chemistry. It could be of great interest to use the *tert*-butoxycarbonyl group (Boc) instead of the methoxycarbonyl group as the former is usually easily removed under fairly mild acidic conditions.

The purpose of this communication is to demonstrate that such *N*-Boc pyrroles are excellent substrates for [4+3] cycloadditions and that an amino group can be easily recovered later, under classical conditions. The cycloadditions have been performed on various α,α′-dibromoketones under the conditions first reported by Mann and de Almeida Barbosa on 2,4-dibromopentan-3-one[5] and the results are given in Table 1.

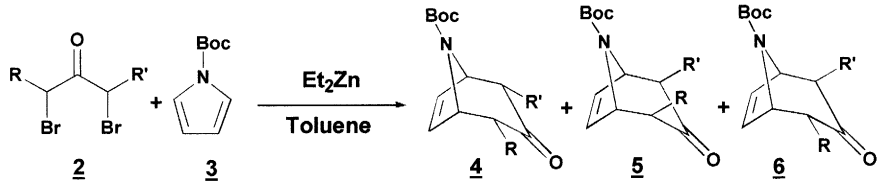



Table 1

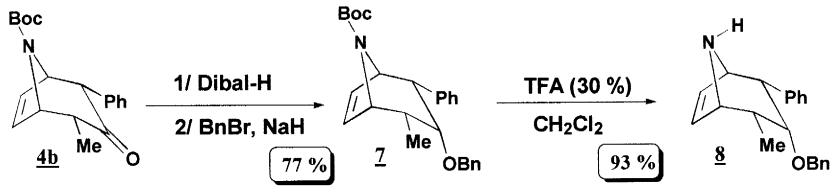
| Entry | R, R' | Ketone (N eq.) | $Et_2Zn$ (N eq.) | Temp./ Time | d.r.[$] 4/ 5/ 6 | Yield*, † |
|---|---|---|---|---|---|---|
| a | $CH_3$, $CH_3$ | 3.8 | 1.0+1.0 | 0°C / 3h<br>17h / R.T. | 92/ 5/ 3 | 63 % |
| b | Ph, $CH_3$ | 1.5 | 1.5 | -10°C / 3h<br>17h / R.T. | 90/ 8/ 2 | 65 % |
| c | Ph, H | 2.0 | 2.0 | -15°C / 3h<br>17h / R.T. | 90/ 10 | 63 % |
| d | $CH_2Ph$, $CH_2Ph$ | 3.0 | 2.0 | 0°C / 3h<br>17h / R.T. | >97/ <3/ <3 | 84 % |
| e | $CH_2Ph$, $CH_2Ph$ | 1.2 | 1.2 | 0°C / 3h<br>17h / R.T. | >97/ <3/ <3 | 25 %‡ |
| f | Ph, Ph | 0.2 | 0.2 | 0°C / 3h<br>17h / R.T. | >97/ <3/ <3 | 12 % |

*Yield of isolated cycloadducts calculated with respect to N-Boc pyrrole, except for entry f where the yield is calculated with respect to the ketone. [$]Diastereomeric ratio established on the crude mixture by GC or $^1$H NMR analysis. † All new compounds gave spectra ($^1$H and $^{13}$C NMR, IR) consistent with their assignated structure and satisfactory accurate mass measurement or combustion analysis[7]. ‡ 70 % of starting dibromoketone was recovered.

In most cases, the cycloadducts are isolated in good yields and the reaction proceeds with very high diastereoselectivity. The only exception is the 1,3-diphenyl-1,3-dibromopropa-3-one (entry f) which gives only 12% of cycloadduct **4f**.† It is worth noting that dibromoketones **2b**, **2c**, **2d**, and **2f** have not previously been used in a [4+3] cycloaddition under these conditions.

† It is worth noting that a similar behaviour was observed starting from methoxycarbonylpyrrole.

Having these compounds in hand, we then had to demonstrate that the deprotection of the nitrogen atom could be performed cleanly. Compound **4b** was used as a model; in agreement with the known sensitivity of tropinones,[8] the direct deprotection causes isomerisation of the C in α of the carbonyl and decomposition of the molecule, therefore, **4b** was transformed to the benzyl ether **7**. Tropane **4b** was first treated with Dibal-H at low temperature to give the corresponding alcohol in good yield and pure diastereoisomeric form. Then the alcohol was protected as a benzyl ether **7**. Next, the Boc group was removed under 'classical' mild conditions; the reaction was instantaneous and afforded the amine **8** in very high yield (Scheme 2).




Scheme 2.

In conclusion, we have shown that the Boc group is compatible with [4+3] cycloaddition reactions under the conditions previously reported with *N*-methoxycarbonylpyrrole and diethylzinc. This group can be easily and cleanly removed under mild conditions. Therefore, it offers a good alternative to the methoxycarbonyl group usually used in these reactions. As this cycloaddition was extended to several dibromoketones, it would be useful both for the total synthesis of various tropanes and for the development of scaffolds for combinatorial chemistry. Work in this field is under progress in our laboratory and will soon be reported.

## Acknowledgements

We thank Dr. P. Guenot for performing the mass spectral experiments, and we thank Dr. F. Bellamy (Laboratoires Fournier, Dijon) for fruitful discussions and financial support.

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7. Compound **4b**: IR (neat): 1700, 1395, 1368, 1172, 1105. $^1$H NMR ($C_7D_8$, 373 K): 7.13–7.00 (m, $5H_{Ar}$), 5.95 (ddd, 1H, J=6.0, 2.5, 1.0 Hz, =CH), 5.92 (ddd, 1H, J=6.0, 2.5, 0.5 Hz, =CH), 4.63 (brs, 1H, N–CH), 4.50 (brs, 1H, N–CH), 3.88 (brd, 1H, J=3.0 Hz, CH–Ph), 2.64 (brdq, 1H, J=~4, ~7 Hz, CH–$CH_3$), 1.43 (s, 9H, $CH_3$), 0.95 (d, 3H, J=7.0 Hz, $CH_3$). $^{13}$C NMR ($C_7D_8$, 373 K): 204.9, 152.3, 137.0, 134.7, 133.8, 130.3, 128.6, 127.4, 80.2, 63.7, 62.6, 62.3, 48.5, 28.8, 11.9. HMRS calcd for $C_{19}H_{23}NO_3$: 313.1678; found: 313.1668. Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; found: C, 72.53; H, 7.56; N, 4.27. Compound **7**: mp: 145°C (hexane). IR ($CCl_4$): 1700, 1695, 1409, 1177, 1100, 1067. $^1$H NMR ($C_7D_8$, 373 K):

7.20–7.15 (m, 2$H_{Ar}$), 7.10–6.99 (m, 6$H_{Ar}$), 6.93–6.89 (m, 2$H_{Ar}$), 6.30 (dd, 1H, J=6.5, 2.5 Hz, =CH), 6.10 (dd, 1H, J=6.5, 2.5 Hz, =CH), 4.57 (brs, 1H, N–CH), 4.31 (brs, 1H, N–CH), 3.75 (d, 1H, J=11.0 Hz, $OCH_2Ph$), 3.49 (d, 1H, J=11.0 Hz, $OCH_2Ph$), 3.48 (brm, 1H, CHOBn), 3.37 (brs, 1H, CH–Ph), 2.30 (ddq, 1H, J=3.0, 4.5, 7.0 Hz, CH–$CH_3$), 1.45 (s, 9H, $OCH_3$), 0.88 (d, 3H, J=7.0 Hz, $CH_3$). $^{13}$C NMR ($C_7D_8$, 373 K): 152.3, 141.3, 139.6, 135.1, 134.4, 129.9, 128.6, 128.3, 127.9, 127.4, 126.8, 82.5, 79.2, 76.7, 62.9, 61.5, 51.9, 38.7, 28.9, 14.2. HMRS calcd for $C_{26}H_{31}NO_3$ : 405.2304; found: 405.2314. Anal. calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.71; N, 3.45; found: C, 76.69; H, 7.78; N, 3.35. Compound **8**: IR ($CCl_4$): 3069, 3065, 3030, 1496, 1453, 1355, 1159, 1096, 1067. $^1$H NMR ($CDCl_3$): 7.34–7.15 (m, 8$H_{Ar}$), 7.01–6.95 (m, 2$H_{Ar}$), 6.62 (dd, 1H, J=6.0, 2.0 Hz, =CH), 6.41 (dd, 1H, J=6.0, 2.0 Hz, =CH), 3.86 (d, 1H, J=11.0 Hz, $OCH_2Ph$), 3.83 (brs, 1H, N–CH), 3.74 (dd, 1H, J=4.5, 4.5 Hz, CHOBn), 3.59 (brdd, 1H, J=∼2, ∼2 Hz, N–CH), 3.51 (d, 1H, J=11.0 Hz, $OCH_2Ph$), 3.47 (dd, 1H, J=4.5, 2.5 Hz, CH–Ph), 2.56 (brs, 1H, NH), 2.37 (ddq, 1H, J=2.5, 4.5, 7.0 Hz, CH–$CH_3$), 0.98 (d, 3H, J=7.0 Hz, $CH_3$). $^{13}$C NMR ($CDCl_3$): 141.3, 139.0, 137.1, 136.7, 129.3, 128.1, 127.9, 127.3, 126.9, 126.3, 81.5, 75.5, 63.7, 62.0, 52.3, 39.0, 15.0. HMRS calcd for $C_{21}H_{23}NO$: 305.1779; found: 305.1776.

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