Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2093–2095

TETRAHEDRON LETTERS

Solid-phase lithiation of 5-carboxyindoles

Jan Tois* and Ari Koskinen

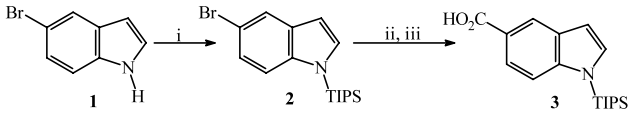
Laboratory of Organic Chemistry, Helsinki University of Technology, 02015 TKK, Finland

Received 17 October 2002; revised 8 January 2003; accepted 17 January 2003

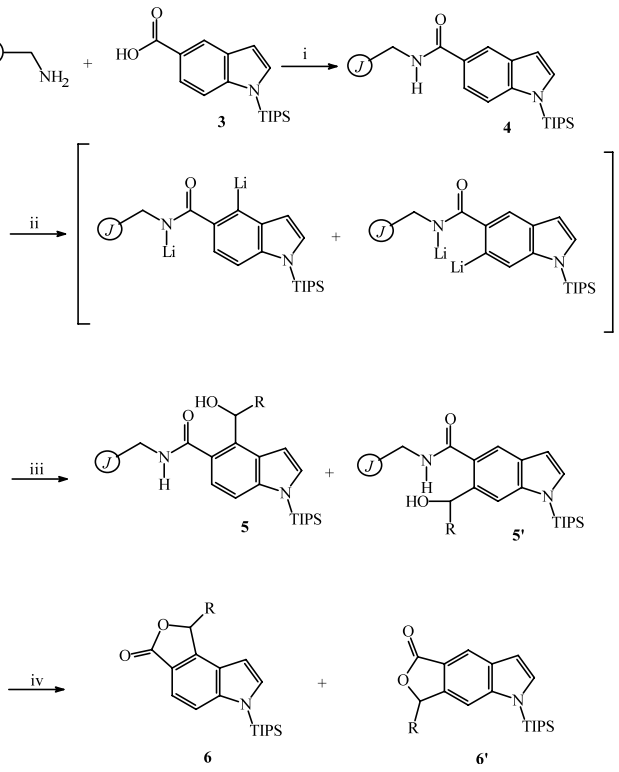
Abstract—Direct functionalization of protected 5-carboxyindole by metalation has been performed for the first time on solid-phase. The indole moiety has been tethered to aminomethylated polytetrahydrofuran cross-linked polystyrene, forming a secondary amide, which functions as a directing metalation group. The *ortho*-lithiated species have been quenched with substituted benzaldehydes affording resin bound alcohols. After cyclative cleavage regioisomeric mixtures of phthalides were obtained in the ratio 80:20.

The 4-substituted indole nucleus is widespread in nature and is found in inter alia the ergot alkaloids.[1] Although methods for the introduction of substituents into the 1-, 2-, and 3-positions of indole are well established,[2] direct functionalization of the carbocyclic ring, and in particular the 4-position, has proven more difficult.[3] Usually the formation of 4-substituted indoles relies on the formation of the pyrrole ring from a suitably adorned benzenoid precursor.[4] It is rare that a direct functionalization of the 4-position can be achieved without a substituent at the 3-position and according to our knowledge there are only two previously reported methods. Widdowson has employed the tricarbonylchromium(0) activation of indole[5] and Snieckus used a directing group at the 5-position[6] in their ring metalation studies. Thallation,[7] mercuration,[8] and lithiation[9] are also efficient methods to functionalize the 4-position but a substituent at the 3-position was present in all cases.

Our group has recently published solid-phase methods for direct functionalization of carboxyindoles at the 3-position[10,11] and we are now screening methods for functionalizing the 4-position. Garibay et al. have recently published their studies of directed *ortho*-lithiation on solid-phase[12,13] and we decided to explore this method in our solid supported experiments.



Scheme 1. *Reagents, conditions and yields*: (i) NaH, TIPSCl, DMF, 0°C–rt, 64%, (ii) *n*-BuLi, THF, −78°C, (iii) CO_2, THF, H^+, −78°C to rt, 68%.



Scheme 2. *Reagents and conditions*: (i) HOBt/DIC, DCM/DMF, rt; (ii) *n*-BuLi, THF, 0°C; (iii) RCHO/THF, 0°C–rt; (iv) toluene, 90°C.

Keywords: carboxyindole; lithiation; solid-phase synthesis.

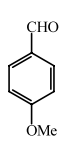
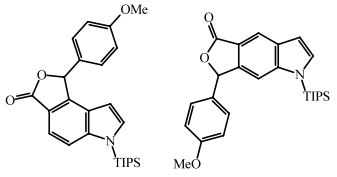
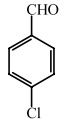
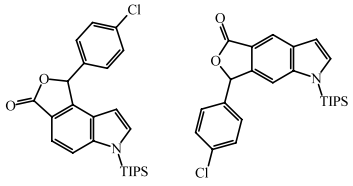
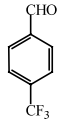
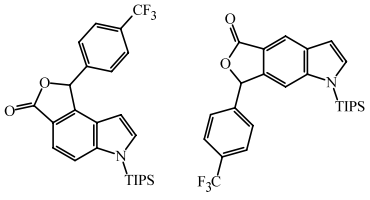
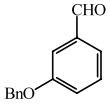
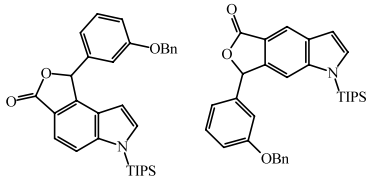
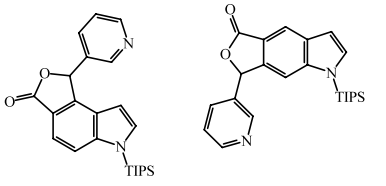
* Corresponding author.

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00175-8

On the basis of previous indole metalation studies[14] we decided to use a bulky *N*-silyl group to prevent 2-deprotonation. The solution phase synthesis of the protected 5-carboxyindole **3**[15] is illustrated in Scheme 1.

The TIPS-protected acid **3** was immobilized onto *J*anda*J*el™-NH_2 resin (Scheme 2) using a standard HOBt/DIC procedure and the corresponding secondary amide **4** was *ortho*-lithiated and quenched with substituted benzaldehydes yielding alcohols **5** and **5′**. Cyclative cleavage occurred when the resin was heated in toluene and phthalides **6** and **6′** were obtained as inseparable mixtures in the ratio 80:20 as determined by NMR.

Table 1. Summarization of aldehydes, products and yields

Aldehydes	Products	Yield[a]
		25 %[b]
		23 %
		31 %
		36 %
		27 %

[a] Isolated yield of two regioisomers (in all cases the isomer where the lithiation has occurred at the 4-position is the main isomer) based on the commercially announced loading.[b] See Ref. 17 for spectral data of main isomer.

Five different aldehydes were examined (see Table 1) and in all cases the product ratio was the same. We tried to improve the regioselectivity by reducing the equivalents of *n*-BuLi and cooling the reaction mixture but similar results were obtained. Garibay reported[13] that 6–8 equiv. of *n*-butyllithium were necessary but in our hands there were no differences in yields when 3 equiv. were used instead of 7 equiv. Boehm and Showalter[16] employed a temperature of 0°C in their directed *ortho*-metalation studies and we also found that this temperature was optimal. When the reaction mixture was cooled to −78°C the formation of the dark coloured dianion was very slow. Increasing the metalation time from 5 to 90 min led, after cleavage, only to traces of the phthalides.

In summary, we have demonstrated that benzenoid ring functionalization of 5-carboxyindoles is possible on solid-phase. Although only moderate regioselectivity was achieved it is obvious that directed *ortho*-metalation is also a powerful tool in solid-phase chemistry. We are now in the process of extending our studies towards different carboxyindoles, different directing groups and other linker-systems.

References

1. Stadler, P. A.; Stutz, P. *The Alkaloids*; Academic Press: New York, 1975; p. 1.
2. Sundberg, R. J. *Indoles*; Academic Press: London, 1996; pp. 89–124.
3. Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267–291.
4. (a) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110; (b) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657–2662.
5. Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325–7334.
6. Griffen, E. J.; Roe, D. G.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484–1485.
7. Somei, M.; Yamada, F.; Naka, K. *Chem. Pharm. Bull.* **1987**, *35*, 1322–1325.
8. Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983–985.
9. Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Freire, G.; Pérez-Castells, J. *Tetrahedron* **2002**, *58*, 5407–5415.
10. Tois, J.; Franzén, R.; Aitio, O.; Laakso, I.; Huuskonen, J.; Taskinen, J. *Comb. Chem. High Throughput Screening* **2001**, *4*, 521–524.
11. Tois, J.; Franzén, R.; Aitio, O.; Laakso, I.; Kylänlahti, I. *J. Comb. Chem.* **2001**, *3*, 542–545.
12. Garibay, P.; Toy, P. H.; Hoeg-Jensen, T.; Janda, K. D. *Synlett* **1999**, 1438–1440.
13. Garibay, P.; Vedsjø, P.; Bergtrup, M.; Hoeg-Jensen, T. *J. Comb. Chem.* **2001**, *3*, 332–340.
14. Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G.; Snieckus, V. *Synthesis* **1991**, 1079–1082.
15. Data for compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, $J=7.5$ Hz, 18 H), 1.76 (sp, $J=7.5$ Hz, 3 H), 6.78 (d, $J=3$ Hz, 1 H), 7.37 (d, $J=3$ Hz, 1 H), 7.58 (d, $J=9$ Hz, 1 H), 7.98 (dd, $J=9$ Hz, $J=1.7$ Hz, 1 H), 8.53 (d,

$J=1.7$ Hz, 1 H); ^{13}C NMR (100 MHz): δ 13.3, 18.4, 106.6, 114.0, 121.4, 123.7, 124.8, 131.6, 133.1, 144.7, 173.8.

16. Boehm, T. L.; Showalter, H. D. *J. Org. Chem.* **1996**, *61*, 6498–6499.
17. Data for main product **6** (R = C_6H_4OMe): ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, $J=7.5$ Hz, 18 H), 1.74 (h, $J=7.5$ Hz, 3 H), 3.83 (s, 3 H), 6.38 (d, $J=3$ Hz, 1 H), 6.53 (s, 1 H), 6.92 (d, $J=7$ Hz, 2 H), 7.29 (d, $J=7$ Hz, 2 H), 7.32 (d, $J=3$ Hz, 1 H), 7.68 (A, J_{AB} = 8.7 Hz, 1 H), 7.72 (B, J_{AB} = 8.7 Hz, 1 H), ^{13}C NMR (100 MHz): δ 12.8, 17.9, 55.3, 82.2, 103.0, 114.2, 115.3, 117.4, 117.7, 125.0, 128.5, 129.2, 133.5, 143.6, 144.4, 160.2, 172.0. MS (EI) m/z 435 $[M]^{+\cdot}$.