Pergamon

Tetrahedron Letters 40 (1999) 4251–4254

TETRAHEDRON
LETTERS

Modified Vilsmeier Reactions of Activated Benzofurans with Indolines: Synthesis of Benzofuran-fused Benzocarbazoles

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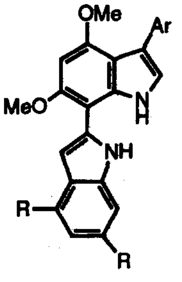
Received 22 February 1999; accepted 6 April 1999

Abstract:

Regioselective reactions of 3-substituted 4,6-dimethoxybenzofurans with indolin-2-ones and triflic anhydride afforded 7- and/or 2-substituted indolo-benzofurans and the latter were cyclised to previously unknown benzofuran-fused benzocarbazoles using palladium (II) acetate in heated acetic acid. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: benzofurans, indolinones, triflic anhydride, palladium (II) acetate

3-Substituted 4,6-dimethoxyindoles have been shown to undergo modified Vilsmeier reactions with indolin-2-ones and phosphoryl chloride or triflic anhydride.[1] 4,6-Dimethoxy-3-methylindole reacted with indolin-2-one and phosphoryl chloride at C7 and C2 to give a mixture of 2,2'- and 2,7'-bi-indolyls in similar proportions. The reaction of 3-aryl-4,6-dimethoxyindoles with indolin-2-ones, however, afforded only 2,7'-bi-indolyls exemplified by structures **1** and **2**.



1) R=H
2) R=OMe

We now wish to report that in contrast to indoles, the treatment of analogous 3-aryl 4,6-dimethoxybenzofurans **3a**[3] and **3b**[3] with indolin-2-one and triflic anhydride give the 2-substituted indolo-benzofurans **4a**[4] and **4b** respectively as major products and the 7-

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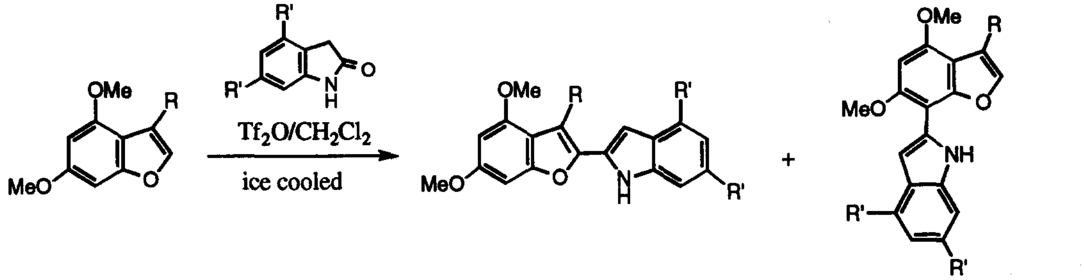
PII: S0040-4039(99)00699-1

substitution products **5a** and **5b** are obtained in low yields due to higher reactivity of the C2 over C7. No reaction took place when benzofuran **3a** was treated with phosphoryl chloride in refluxing dichloromethane for 72 h. When indolin-2-one was replaced by the analogous 4,6-dimethoxyindolin-2-one[1,2] in the presence of triflic anhydride the yield of the corresponding 2-indolylbenzofuran **4d** was dramatically reduced to 17% (27% based on recovered starting material). Other products were suspected to be polymeric compounds but these were not isolated. The presence of the two methoxy groups at indole C4 and C6 of the resulting 2-indolylbenzofuran **4d** activates the 7-position of the indole segment which could probably result in further reactions of 4,6-dimethoxyindolin-2-one at this position to give ultimately the suspected polymeric material.

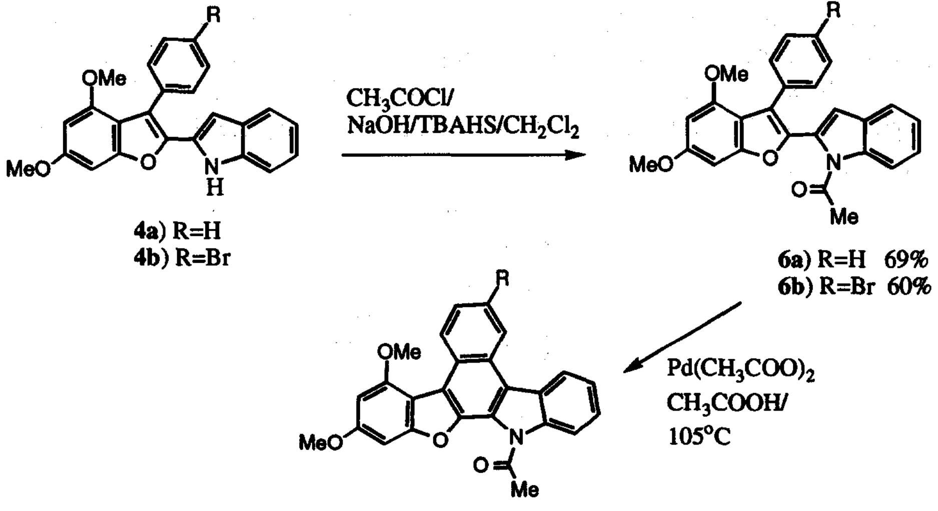


3a) R=Ph
3b) R=4-BrC_6H_4
3c) R=*t*-Bu

4a) R=Ph, R'=H 58%
4b) R=4-BrC_6H_4, R'=H 37%
4c) R=*t*-Bu, R'=H 0%
4d) R=Ph, R'=OMe 17%

5a) R=Ph, R'=H 10%
5b) R=4-BrC_6H_4, R'=H 28%
5c) R=*t*-Bu, R'=H 87%
5d) R=Ph, R'=OMe 0%

In contrast to the above results, the reaction of 3-*t*-butyl-4,6-dimethoxybenzofuran **3c**[3] with indolin-2-one under the same conditions afforded only the 7-indolylbenzofuran **5c**[5] in high yield. It appears that the reactivity of benzofuran C2 towards indolin-2-one is strongly retarded due to the steric hindrance effect of the tertiary butyl group and hence the C7 becomes the preferred site of the reaction.



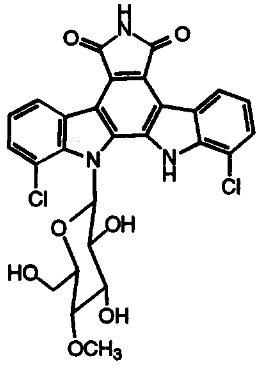
4a) R=H
4b) R=Br

6a) R=H 69%
6b) R=Br 60%

7a) R=H 57%
7b) R=Br 54%

Compounds **4a** and **4b** were acetylated using acetyl chloride in the presence of crushed sodium hydroxide and tetrabutylammonium hydrogensulfate in dichloromethane. The resulting protected indolo-benzofuran **6a**[6] and **6b** were then cyclised to benzofuran-fused benzocarbazoles **7a**[7] and **7b** using palladium (II) acetate in acetic acid at 105°C.

The similarity of the backbone structure of benzocarbazoles **7a** and **7b** to indolocarbazole chromophore of rebeccamycin **8**[8,9] and staurosporine **9** and derivatives[10] raises interest to study their potential antitumor and antibiotic activities.



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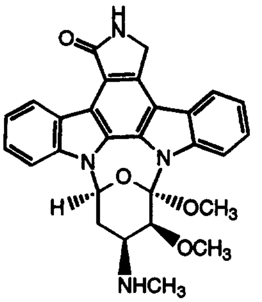

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Acknowledgment

The financial support from the Australian Research Council is gratefully acknowledged.

References and Notes

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[4] Data for **4a**: m.p. 67-69°C (from ethyl acetate/light petroleum). (Found C, 78.1; H, 5.1; N. 3.8. $C_{24}H_{19}NO_3$ requires C, 78.0; H, 5.2, N, 3.8%). ^{1}H NMR spectrum ($CDCl_3$): δ 3.71 3.91 (6H, 2s, OMe); 6.40 (1H, s broad, benzofuran H5); 6.76 (2H, s broad, benzofuran H7, indole H3); 7.18-7.71 (9H, m, aryl); 8.36 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.2, 55.6 (OMe); 87.9, 94.7, 100.8, 110.7, 120.1, 120.5, 122.5, 127.8, 128.1, 130.5 (12 x aryl CH); 112.7, 116.9, 128.3, 128.7, 132.7, 135.9, 142.7, 154.6, 155.8, 159.3 (aryl C). Mass spectrum: m/z 369 (M, 100%), 354 (44).

[5] Data for **5c**: m.p. 223-225°C (from ethyl acetate/light petroleum). (Found: C, 75.8; H, 7.0, N, 3.9. $C_{22}H_{23}NO_3$ requires C, 75.6; H, 6.7; N, 4.0%). ^{1}H NMR spectrum: δ 1.46 (9H, s, CMe_3); 4.01, 4.07 (6H, 2s, OMe); 6.51 (1H, s, benzofuran H5); 7.11-7.70 (6H, m, aryl); 9.84 (1H, s, NH). ^{13}C NMR spectrum: δ 30.2 ($C\underline{Me}_3$); 30.8 ($\underline{C}Me_3$); 55.1, 57.1 (OMe); 91.4 (benzofuran C5); 102.8, 110.5, 119.4, 120.2, 121.4, 138.1 (aryl CH); 100.2, 112.0, 128.6, 131.0, 131.3, 135.3, 152.4, 155.0, 155.2 (aryl C). Mass spectrum: m/z 513 (M, 5%), 385(34), 383 (100), 349 (100).

[6] Data for **6a**: m.p. 146-148°C (from ethyl acetate/light petroleum). (Found C, 75.6; H, 5.2, 3.5. $C_{26}H_{21}NO_4$ requires C, 75.9, 5.2, 3.4%). ^{1}H NMR spectrum ($CDCl_3$): δ 2.34 (3H, s, COMe); 3.78, 3.90 (6H, 2s, OMe); 6.42 (1H, d, J 2.1 Hz, benzofuran H5); 6.66 (1H, s, indole H3); 6.73 (1H, d, J 2.1 Hz,

benzofuran H7) ; 7.26-8.47 (9H, m, aryl). ^{13}C NMR spectrum ($CDCl_3$): δ 25.1 ($CO\underline{C}H_3$); 55.4, 55.7 (OMe); 88.0, 95.1 (benzofuran C5, benzofuran C7); 115.1, 116.4, 120.9, 123.6, 125.8, 127.3, 127.7, 130.2 (10 x aryl CH); 111.2, 122.0, 128.0, 128.5, 131.8, 137.4, 141.6, 154.9, 156.6, 160.0 (aryl C); 170.4 (CO). Mass spectrum: m/z 411 (M, 100%), 369(100), 354 (69).

[7] Data for **7a**: m.p. 185-187°C (from ethyl acetate/light petroleum). (Found C, 76.2; H, 4.9; N, 3.2. $C_{26}H_{19}NO_4$ requires C, 76.3; H, 4.7, N, 3.4%). ^{1}H NMR ($CDCl_3$): δ 2.89 (3H, s, COMe); 3.87, 4.01 (6H, 2s, OMe); 6.39 (1H, d, J 2.1 Hz, benzofuran H5); 6.71 (1H, d, J 2.1 Hz, benzofuran H7); 7.26-8.51 (6H, m, aryl); 8.77, 9.50 (2H, 2d, J 8.2 Hz, aryl). ^{13}C NMR spectrum ($CDCl_3$): δ 27.3 ($CO\underline{C}H_3$); 55.7 (2 x OMe); 88.4, 95.0 (benzofuran C5, benzofuran C7); 115.4, 121.6, 123.9, 124.6, 125.3, 126.2, 128.3, (8 x aryl CH); 108.5, 118.6, 119.8, 123.5, 126.7, 127.9, 129.8, 139.3, 141.4, 154.5, 157.8, 160.2 (aryl C); 171.7 (CO). Mass spectrum: m/z 409 (M, 95%), 367(100), 352 (61), 309 (34).

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