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THE PREPARATION OF 9-ALKYLTHIOFLUORENES FROM BIPHENYL-2-CARBOXALDEHYDES

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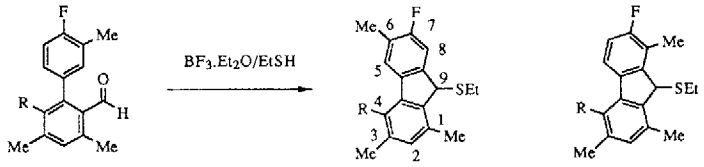
Summary: Upon treatment with ethanethiol and boron trifluoride etherate, the biphenyl-2-carboxaldehyde 1 has been found to undergo facile cyclization to the 9-ethylthiofluorenes 2.

During the course of a recent synthetic study[1] we discovered that treatment of compound **1** with ethanethiol and boron trifluoride etherate led to benzyl ether removal[2] and concomitant cyclization to the fluorenes **2** (**2a**:**2b**, 3:1),[3] in quantitative yield (Scheme 1).[4]

Scheme 1



1. R= $(CH_2)_3OCH_2Ph$
3. R=H

2a. R= $(CH_2)_3OH$
4a. R=H

2b. R= $(CH_2)_3OH$
4b. R=H

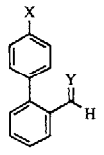
In view of the mild conditions required for the cyclization (*vide infra*) and the ready accessibility of variously substituted biphenyls,[5] we were prompted to investigate this reaction in more detail as a potential route to fluorene derivatives.

Thus treatment of aldehyde **3**[6] in dry dichloromethane at room temperature with EtSH (10 eq.)/$BF_3.Et_2O$ (8 eq.) led rapidly (30 min) to fluorenes **4** (**4a**:**4b**, 3:1) in 94% yield. Under identical conditions biphenyl-2-carboxaldehyde **5** cyclized more slowly (16h, r.t.) to give 9-ethylthiofluorene **6** in 93% yield.[7] The aldehydes **3** and **5** were recovered unchanged after 24 hours when exposed to these reaction conditions in the *absence* of ethanethiol.

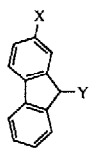
The thioacetal **7** was isolated in 80% yield when aldehyde **5** was treated with EtSH (10 eq.)/$BF_3.Et_2O$ (8 eq.) in CH_2Cl_2 at room temperature for 5 min. When thioacetal **7** was retreated with $BF_3.Et_2O$ (8 eq.) in the *absence* of ethanethiol, fluorene **6** was produced at a *markedly accelerated rate* in comparison with the direct preparation from **5** described above. The rate of formation of fluorene **6** from aldehyde **5** was also significantly enhanced (30 min, r.t.) when the quantity of thiol used in the original procedure was reduced to 1.2 equivalents.[8] These observations are most consistent with a mechanism in which a thionium intermediate **8** is involved in the cyclization.[9]

It is of further interest that the cyclic thioacetal **9**[10] was recovered unchanged when treated with $BF_3.Et_2O$ (8 eq.) in CH_2Cl_2 (24h, r.t.). Also, the dimethylacetal **10**[11] did not undergo cyclization to 9-methoxyfluorene **11** when treated with $BF_3.Et_2O$ (8 eq.) in CH_2Cl_2 (20h, r.t.). After aqueous work up the aldehyde **5** was recovered in excellent yield.

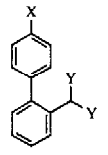
While the reaction is not restricted to substrates possessing favorably disposed electron-donating substituents on the ring undergoing electrophilic substitution, as might be anticipated, electron withdrawing substituents do impede cyclization. Thus prolonged treatment of aldehyde **12**[12] with EtSH (10 eq.)/$BF_3.Et_2O$ (8 eq.) (18h) at ambient temperature led only to the formation of thioacetal **13**. When thioacetal **13** was treated with $BF_3.Et_2O$ (4 eq.) in benzene (ca. 0.1M) at reflux, under a stream of argon for 20 min, fluorene **14** was obtained (45% from **12**).[13]



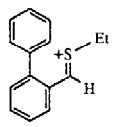
5. X=H, Y=O
12. X=CF_3, Y=O



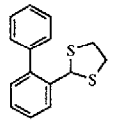
6. X=H, Y=SEt
11. X=H, Y=OMe
14. X=CF_3, Y=SEt



7. X=H, Y=SEt
10. X=H, Y=OMe
13. X=CF_3, Y=SEt



8.



9.

In conclusion, we have discovered a facile cyclization of biphenyl-2-carboxaldehydes which affords a useful synthetic approach to 9-alkylthiofluorenes. The 9-alkylthiofluorenes may themselves be further elaborated through alkylation[14] and the thioalkyl substituent removed through Raney nickel desulfurization.[7]

Acknowledgement: We should like to thank M. Huddleston for high resolution mass spectra, E.A. Reich for elemental analysis and Drs. B.W. Metcalf and J. Luengo for helpful discussions.

References:

1. Leber, J.D.; Elliott, J.D., Manuscript in preparation.
2. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E., J. Org. Chem., 1979, **44**, 1661.
3. Ratio determined by 250MHz ^{1}H-NMR ($CDCl_3$) Compound **2a**: δ 7.32 (d, J=9.6Hz, H-8), 4.76 ppm (s, H-9). Compound **2b**: δ 6.96 (dd, J=8.9,9.7Hz, H-6), 4.69 ppm (s, H-9)
4. All compounds had spectral characteristics (^{1}H-NMR, IR and MS) compatible with the assigned structure. All new compounds gave a satisfactory combustion analysis or high resolution mass spectrum.
5. a) Murahashi, S.; Tamba, Y.; Yamamura, M.; Yoshimura, N., J. Org. Chem., 1978, **43**, 4099. b) Meyers, A.I.; Gabel, R.; Mihelich, E., J. Org. Chem., 1978, **43**, 1372. c) Echavarren, A.M.; Stille, J.K., J. Am. Chem. Soc., 1987, **109**, 5478.
6. Stokker, G.E.; Alberts, A.W.; Anderson, P.S.; Cragoe Jr., E.J.; Deanna, A.A.; Gilfillan, J.L.; Hirshfield, J.; Holtz, W.J.; Hoffman, W.F.; Huff, J.W.; Lee, T.J.; Novello, F.C.; Prugh, J.D.; Rooney, C.S.; Smith, R.L.; Willard, A.K., J. Med. Chem., 1986, **29**, 170.
7. Desulfurization with Raney nickel afforded fluorene, identical in all respects (^{1}H-NMR, IR, MS and m.p.) with an authentic sample (Aldrich). Mixed m.p. 112-114°C
8. An optimal procedure has been developed. To a stirred solution of aldehyde **5** (70mg, 0.38mmol.) in dry CH_2Cl_2 (0.5ml.) under argon was added ethanethiol (34μl, 0.46mmol.) followed by boron trifluoride etherate (127μl, 1.03mmol.). After 20 min the reaction was quenched by the addition of water. Conventional work up and column chromatography gave 9-ethylthiofluorene (77mg, 90%) as a white solid m.p. 45-46°C (Lit.[15] 45.5-46.5°C)
9. For examples of other carbocyclization processes involving thionium species see: Trost, B.M.; Murayama, E., J. Am. Chem. Soc., 1981, **103**, 6529 and references therein.
10. Prepared by treatment of aldehyde **5** with ethane-1,2-dithiol (4 eq.)and $BF_3.Et_2O$ (3 eq.) (CH_2Cl_2, r.t., 10 min, 91% yield).
11. Prepared by treatment of aldehyde **5** with 2,2-dimethoxypropane and a catalytic quantity of p-toluene sulfonic acid at r.t. for 18h (89%).
12. Eaddy III, John F., U.S. Patent 4,578,522. Chem. Abs., 1986, **105**, 6311k.
13. The only other identifiable product was 2-ethylthiomethyl-4'-trifluoromethyl-biphenyl (15%).
14. Ikehira, H.; Tanimoto, S.; Oida, T., J.C.S. Perkin I, 1984, 1223.
15. Nakanishi, W.; Kusuyama, Y.; Ikeda, Y.; Oki, M., J.C.S. Perkin II, 1986, 799.

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