Pergamon

Tetrahedron Letters, Vol. 37, No. 10, pp. 1523-1526, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00098-6

Reversible Friedel-Crafts Acylations of 3-Alkyl-1-(Phenylsulfonyl)pyrroles: Application to the Synthesis of an Ant Trail Pheromone

Dong Xiao, Jeffrey A. Schreier, James H. Cook, Paul G. Seybold and Daniel M. Ketcha*

Department of Chemistry, Wright State University, Dayton, OH 45435

Abstract: *Friedel-Crafts acylations of 3-alkyl-1-(phenylsulfonyl)pyrroles appear to be kinetically favored at the adjacent C-2 position but rearrangement to the C-5 position can occur after prolonged reaction times. This reversible Friedel-Crafts methodology has been employed for the synthesis of the ant trail pheromone, methyl 4-methylpyrrole-2-carboxylate.*

Pyrroles normally undergo substitution at the C-2 position, however, 1-(phenylsulfonyl)pyrrole has been shown to display a *tunable reactivity* in Friedel-Crafts acylations wherein the site of substitution is largely controlled by the acid catalyst employed.[1] This differential reactivity has been interpreted[1c] in terms of the hard and soft acids and bases (HSAB) principle[2] and takes into account the facts that while CNDO calculations indicate the greater negative charge in 1-(phenylsulfonyl)pyrrole is located on C-3, the higher HOMO coefficient is at C-2.[1c] Thus, invoking Klopman's general treatment of chemical reactivity,[3] reaction with hard electrophiles is apparently *charge controlled* and occurs at C-3, whereas reaction with soft electrophiles is *frontier orbital controlled* and occurs at C-2.

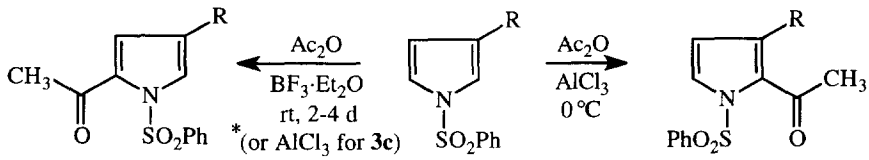
However, not all additions to 1-(phenylsulfonyl)pyrrole occur with a high degree of regiocontrol. For instance, in contrast to acylation reactions, Friedel-Crafts alkylations proceed in low yield and produce mixtures of isomers.[1d] Thus, a two step maneuver involving regioselective Friedel-Crafts acylation followed by reductive deoxygenation appears to represent the method of choice for the synthesis of alkyl derivatives. Recently, we reported that *tert*-butylamine borane complex ($^{t}BuNH_2 \cdot BH_3$) in the presence of aluminum chloride ($AlCl_3$) is capable of reducing a variety of 2- and 3-acyl-1-(phenylsulfonyl)pyrroles to the corresponding alkyl derivatives.[4] The fact that this acylation-reduction protocol proceeds without loss of the protecting group or acid mediated rearrangement of substituents now allows for a more detailed examination of the role of the protecting group in directing electrophilic additions to alkyl-1-(phenylsulfonyl)pyrroles as a route to polysubstituted pyrroles. The low yields observed in Friedel-Crafts alkylations combined with the reported difficulty in separating the isomeric alkyl derivatives have apparently served to discourage extensive efforts along these lines.

While no comprehensive studies on the regioselectivity of Friedel-Crafts acylations of alkyl-1-(phenyl--sulfonyl)pyrroles have been reported, in a limited study Anderson et al.[1d] found that acylations of several 3-alkyl derivatives (Et-, ^{i}Pr-, ^{t}Bu-) using acetyl chloride/$AlCl_3$ (0 °C to rt, 42 h) in dichloromethane afforded predominantly the 5-acetyl isomers. However, ^{13}C NMR chemical shifts of 3-alkyl-1-(phenylsulfonyl)pyrroles (~4.7 ppm upfield)[5] indicate that the greatest shielding (and inferentially the greater pi-density)[6] occurs at C-2,

and our simple HMO calculations for 3-methylpyrrole itself indicate that the adjacent C-2 position is more pi-electron rich than the C-5 position. It was thus suspected that electrophilic attack upon 3-alkylpyrrole derivatives should take place preferentially at the 2 position, and that the isomers obtained by Anderson may have been the result of initial kinetic[7] acylation at the adjacent C-2 position followed by rearrangement of the acyl group to afford the presumably more stable 3-alkyl-5-acyl product.

Though not unprecedented in the chemistry of pyrroles,[8] such facile rearrangements were somewhat unexpected since in order to rule out rearrangements as a rationale for the β-selectivity observed in acylations of 1-(phenylsulfonyl)pyrrole, Kakushima and Rokach[1c] had earlier demonstrated that addition of $AlCl_3$ (1 eq) at 25 °C to 2-acetyl-1-(phenylsulfonyl)pyrrole produced a stable (24 h, NMR) complex from which the starting material could be regenerated upon aqueous workup.

When we conducted the acylation of 3-ethyl-1-(phenylsulfonyl)pyrrole (**1a**) with acetic anhydride/$AlCl_3$ (0 °C), we found this reaction to be complete within 30 min (tlc) and obtained a 76% yield of 2-acetyl-3-ethyl-1-(phenylsulfonyl)pyrrole (**2a**) (Scheme 1). Likewise, acylation of the 3-benzyl derivative **1b** under the same conditions (0 °C, 2 h) afforded mainly the 2,3-isomer **2b** (48%) along with some of the 3,5-isomer. The observation of mainly 2,3-disubstituted products is thus consistent with a general pattern of reactivity exhibited by 3-alkyl pyrroles; for instance, 3-methylpyrrole is known to undergo protonation[9] as well as formylation[10] predominantly at the adjacent α-site. However, under the above conditions, acylation of the 3-*tert*-butyl derivative **1c** was found to occur only at the opposite α-position yielding **3c** presumably for steric reasons.



3a : 60%
3b : 75%
3c : 55%*

1a : R = Et-
1b : R = $PhCH_2$-
1c : R = ^{t}Bu-

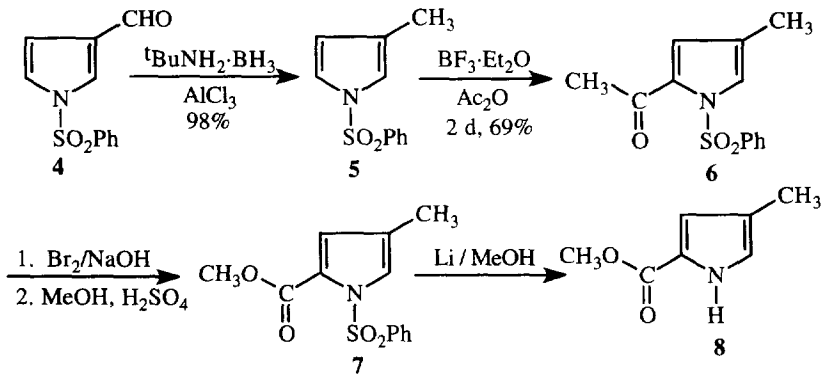
2a : 76%
2b : 48%

Scheme 1

In order to obtain the 3,5-disubstituted products observed by Anderson, we sought optimal conditions for effecting this putative rearrangement process regioselectively. At present, it appears that acetic anhydride in the presence of boron trifluoride etherate (BF_3·Et_2O) for periods of 2-4 d is the most efficient means of obtaining the 3,5-disubstitution pattern. Thus, acylation of **1a** and **1b** using acetic anhydride/BF_3·Et_2O yielded mainly **3a** and **3b** in yields of 60% and 75% respectively (Scheme 1).

With a reliable route to 3-alkyl-5-acylpyrroles secured, we next sought to apply this strategy to the synthesis of the ant trail pheromone, methyl 4-methylpyrrole-2-carboxylate.[11,12] To this end, reduction of 1-(phenylsulfonyl)pyrrole-3-carboxaldehyde (**4**)[13] with ^{t}BuNH_2·BH_3/$AlCl_3$ afforded 3-methyl-1-(phenylsulfonyl)pyrrole (**5**) in 98% yield (Scheme 2). Under catalysis of BF_3·Et_2O, acetylation of **5** with acetic anhydride for 2 h gave a mixture of 5-acetyl-3-methyl-1-(phenylsulfonyl)pyrrole (**6**) and the 2-acetyl-3-methyl

isomer (6:4 from NMR). However, if the reaction were run for 48 h, the more stable isomer[14] **6** could be obtained in 69% yield. Hypohalite oxidation[15] followed by Fischer esterification then afforded the methyl carboxylate **7** in 37% after the two steps. Finally, removal of the N-phenylsulfonyl group using lithium in methanol under reflux furnished the natural product **8** in 94% yield.



Scheme 2

In conclusion, while the regioselectivities of Friedel-Crafts acylations of 1-(phenylsulfonyl)pyrrole are largely controlled by the nature of the electrophile, this factor may be of lesser importance in determining the site of substitution in the case of alkyl derivatives. However, control of the site of substitution in Friedel-Crafts acylations of 3-alkyl derivatives can be achieved under the proper reaction conditions, and this reversible Friedel-Crafts acylation strategy can be employed for the synthesis of alkaloid target molecules.[16]

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for support of this research.

REFERENCES AND NOTES

1. (a) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, 22, 4899-4900. (b) Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, 22, 4901-4904. (c) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, 48, 3214-3219. (d) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, 63, 896-902.
2. (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, 85, 3533-3539. (b) Pearson, R. G. *Science* **1966**, 151, 172-177. (c) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, 89, 1827-1836. (c) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, 105, 7512.
3. Klopman, G. *J. Am. Chem. Soc.* **1968**, 90, 223-234.
4. Ketcha, D. M.; Carpenter, K. P.; Atkinson, S. T.; Rajagopalan, H. R. *Synth. Commun.* **1990**, 20, 1647-1655
5. Ketcha, D. M., unpublished results.
6. Spiesecke, H.; Schneider, W. G. *Tetrahedron Lett.* **1961**, 468-472.

7. *Cf.*: (a) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1333-1336. (b) Kruse, L. I.; DeBrosse, C. W.; Kruse, C. H. *J. Am. Chem. Soc.* **1985**, 107, 5435-5442.
8. For examples of rearrangement processes of pyrroles, see: (a) Kakushima, M.; Frenette, R. *J. Org. Chem.* **1984**, 49, 2025-2027. (b) Carmona, O.; Greenhouse, R.; Landeros, R.; Muchowski, J. M. *J. Org. Chem.* **1980**, 45, 5336-5339. (c) Carson, J. R.; Davis, N. M. *J. Org. Chem.* **1981**, 46, 839-843.
9. Chiang, Y.; Whipple, E. B. *J. Am. Chem. Soc.* **1963**, 85, 2763-2767.
10. Hinman, R. L.; Theodoropulos, S. J. *J. Org. Chem.* **1963**, 28, 3052-3058.
11. (a) Tumlinson, J. H.; Silverstein, R. M.; Moser, J. C.; Brownlee, R. G.; Ruth, J. M. *Nature (London)* **1971**, 234, 348-349. (b) Do Nascimento, R. R.; Morgan, E. D.; Moreira, D. D. O, Della Lucia, T. M. C. *J. Chem. Ecol.* **1994**, 20, 1719-1724.
12. For previous syntheses of methyl 4-methylpyrrole-2-carboxylate, see: (a) Rapoport, H.; Bordner, J. *J. Org. Chem.* **1964**, 29, 2727-2731 (b) Sonnet, P. E. *J. Med. Chem.* **1972**, 15, 97-98 (c) Walizei, G. H.; Breitmaier, E. *Synthesis* **1989**, 337-340 (d) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron Lett.* **1990**, 46, 7587-798 (e) Cornforth, J.; Ming-hui, D. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1459-1462 (e) Zimmer, R.; Collas, M.; Roth, M.; Reissig, H. *Liebigs Ann. Chem.* **1992**, 709-714.
13. (a) Xiao, D.; Ketcha, D. M. *Org. Prep. Proced. Int.* **1995**, 27, 503-506. (b) Fuji, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1992**, 2338-2343. (c) Hamdan, A.; Wasley, J. W. F. *Synth. Commun.* **1983**, 13, 741-744.
14. Semiempirical AM1[a,b] all-valence-electron molecular orbital calculations of total energy indicate that the 3,5-form is more stable than the 2,3-form by ca. 1.2 kcal/mol. Differences in overall stabilization arise because the 3-methyl group forces the 2-acetyl substituent to assume energetically unfavorable orientations: (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, 107, 3902-3909. (b) Stewart, J. J. P., MOPAC, QCPE Program 445, ver. 6.0, Quantum Chemistry Program Exchange, Indiana Univ., Bloomington, IN 47405.
15. (a) Kamogawa, H.; Nakata, T.; Ohori, S.; Komatsu, S. *Bull. Chem. Soc. Jpn.* **1991**, 64, 1066-1068. (b) Gaare, K.; Repstad, T.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, 47, 57-62. (c) Cativiela, C; Garcia, J. I. *Org. Prep. Proced. Int.*, **1986**, 18, 283-285.
16. All new compounds were fully characterized by IR, NMR ($CDCl_3$), and elemental analysis. Selected physical and spectral properties follow:
2a: mp 98-99 °C (lit.[1d] mp 98-99 °C); ^{13}C NMR δ 190.4, 139.4, 138.6, 133.4, 131.5, 128.8, 127.9, 127.4, 113.4, 30.6, 20.8, 14.5;
2b: mp 111-113 °C; ^{1}H NMR δ 7.06-7.69 (m, 11H), 6.06 (d, 1H, J = 3.4 Hz), 3.93 (s, 2H), 2.46 (s, 3H); ^{13}C NMR δ 139.0, 138.7, 134.9, 133.6, 128.8, 128.6, 128.5, 127.7, 127.3, 126.5, 115.1, 33.3, 30.3;
3a: mp 94-95 °C (lit.[1d] mp 94-95 °C); ^{13}C NMR δ 185.5, 139.2, 133.3, 133.0, 128.4, 127.8, 127.6, 126.7, 124.5, 26.7, 19.4, 14.3;
3b: mp 119-120.5 °C; ^{1}H NMR δ 7.99 (m, 2H), 7.20-7.97 (m, 9H), 6.86 (d, 1H, J = 1.9 Hz), 3.82 (s, 2H), 2.28 (s, 3H); ^{13}C NMR δ 185.8, 139.5, 139.1, 133.5, 128.7, 128.6, 128.1, 127.9, 126.6, 125.1, 124.9, 32.7, 26.8;
5: mp 55-56 °C; ^{1}H NMR δ 7.83 (m, 2H), 7.43-7.62 (m, 3H), 7.07 (m, 1H), 6.89 (d, 1H, J = 8.7 Hz), 6.12 (d, 1H, J = 3.4 Hz), 2.02 (s, 3H); ^{13}C NMR δ 139.2, 133.5, 129.1, 126.6, 124.6, 120.9, 117.8, 115.9, 11.8;
6: mp 124.5-126.5 °C; ^{1}H NMR δ 7.99 (m, 2H), 7.46-7.63 (m, 4H), 6.90 (d, 1H, J = 1.9 Hz), 2.31 (s, 3H), 2.12 (s, 3H); ^{13}C NMR δ 185.6, 139.2, 133.4, 133.0, 128.6, 128.0, 126.0, 120.8, 26.8, 11.4;
7: mp 106-108 °C; ^{1}H NMR δ 7.95 (m, 2H), 7.48-7.61 (m,4H), 6.90 (d, 1H, J = 2.0 Hz), 3.70 (s, 3H), 2.09 (s, 3H); ^{13}C NMR δ 159.1, 139.2, 133.6, 128.8, 127.9, 126.7, 125.1, 124.6, 121.0, 51.6, 11.4;
8: mp 71-72 °C (lit.[12a] mp 73-74 °C); ^{13}C NMR δ 161.6, 121.3, 120.9, 116.4, 51.3, 11.6.

(*Received in USA* 3 *November* 1995; *accepted* 21 *December* 1995)