Pergamon

Tetrahedron Letters, Vol. 36, No. 37, pp. 6739-6742, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01328-8

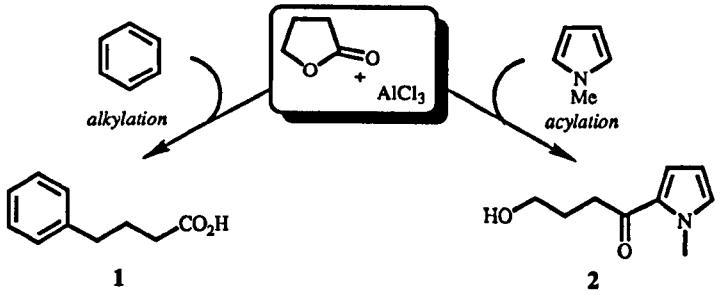
A Dichotomy in the Friedel-Crafts Reactions of Lactones Provides a Convenient New Route to 2-Acylated Pyrroles and Tetrahydroindolones.

David C. Harrowven* and Richard F. Dainty

Department of Chemistry, The University, Southampton, S017 1BJ, UK

Abstract: In striking contrast to arenes, N-methylpyrrole undergoes Friedel-Crafts acylation with lactones. The reaction is most efficient with γ- and δ-lactones; ε-lactones proceed with poor overall conversion while β-lactones display poor selectivity. γ-Alkyl-γ-lactones readily yield 4,5,6,7-tetrahydroindol-7-ones through a sequence analogous to the Truce-Olson annulation.

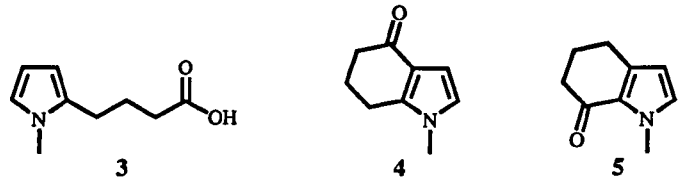
The Lewis acid mediated union of arenes with lactones was first described by Eijkmann in 1904.[1] In the subsequent years several extensions have been reported and method has become widely used for the preparation of arylalkanoic acids.[2-6] While much effort has focused on delineating the scope of this reaction with respect to the lactone,[2] the arene[3] and the Lewis acid,[4] scant attention has been paid to its use as a means of elaborating heteroaromatic compounds.[5] We therefore decided to extend our current study to address this omission.[6] In this *letter* we wish to report some of our preliminary findings which have revealed a striking dichotomy between the Friedel-Crafts reactions of pyrroles and arenes with lactones.[7]



1 2

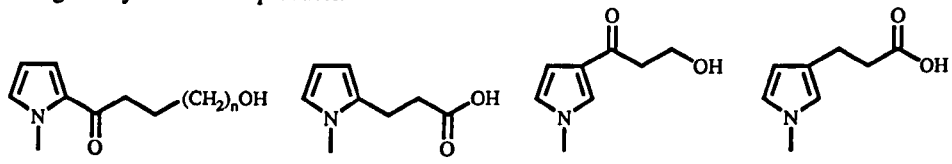
Scheme 1

We first examined the coupling of *N*-methylpyrrole and γ-butyrolactone.[8] Unexpectedly, heating a chloroform solution of these materials at 60°C for 3h provided the *acylated* product **2** (80%) rather than the anticipated carboxylic acid **3** (Scheme 1).[9] Two minor components, the tetrahydroindolones **4** (8%) and **5** (9%) were also isolated.[10]



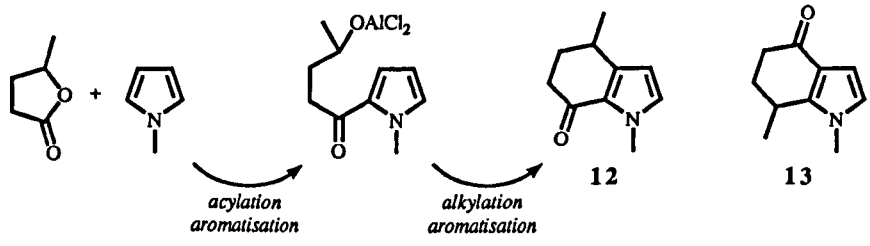
3 4 5

To explore further the scope of this method, we next examined the effect of the lactone ring size upon the outcome of the reaction. With β-propiolactone the reaction was found to be much less selective; the aforementioned conditions giving rise to a 5:2 mixture of the 2- and 3-acylated pyrroles **6** and **10** in a disappointing 28% yield. The overall yield was substantially improved when the reaction was conducted at -30°C with $TiCl_4$, however the pyrrole **6** was now accompanied by the alkylation products **9** and **11** (67%, **6**:**9**:**11**, 4:3:1). With δ-valerolactone (60°C, $CHCl_3$, 3h) the reaction was cleaner, furnishing the ketone **7** in reasonable yield (58%) together with some recovered lactone (20%). Similarly, the homologous ketone **8** could be accessed from ε-capriolactone (60°C, $CHCl_3$, 4h), albeit with poor overall conversion (26% + 65% recovered lactone). Prolonged reaction times with the lactones were found to be deleterious. Esters failed to give any substitution products.



6 n=0, **7** n=2, **8** n=3 **9** **10** **11**

We then examined the possibility of effecting a *reversed* Truce - Olson annulation of *N*-methylpyrrole using this methodology (*viz.* Scheme 2).[11] Initial attempts to optimise production of **4** and **5** from γ-butyrolactone met with limited success. However, simply refluxing a chloroform solution containing γ-valerolactone, *N*-methylpyrrole and aluminium trichloride for 1h furnished, in 65% yield, the tetrahydroindolone **12**. This was accompanied by lesser quantities of the regioisomer **13** (26%).

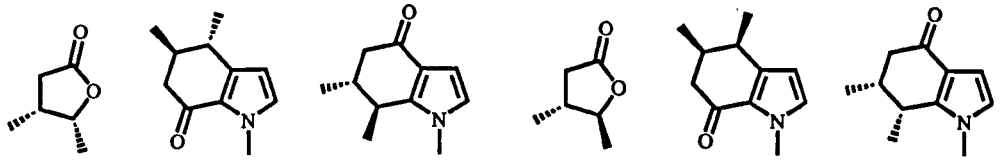


12 **13**

Scheme 2

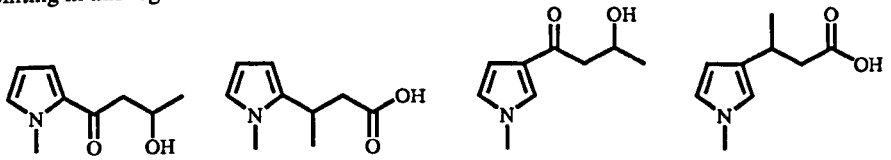
Similarly, treatment of *N*-methylpyrrole in an analogous fashion with the *cis*-lactone **14** produced a mixture of the *trans*-diastereoisomers **15** (45%) and **16** (22%). When this reaction was performed using a 1:1 mixture of the *cis*- and *trans*- lactones **14** and **17**, this ratio was reflected in the resulting mixture of tetrahydroindolones. This suggests that the ring closure step proceeds with almost complete inversion of

configuration at the stereogenic centre. By way of comparison, the corresponding annulation of arenes gives *c.a.* 50% net inversion.[12]



14 **15** **16** **17** **18** **19**

Attempts to effect a pentannulation of *N*-methylpyrrole with β-butyrolactone were unsuccessful.[13] Indeed, in all cases studied a mixture of mono-acylated and alkylated products resulted. A summary of some key experiments is presented in Table 1. Terminally substituted δ- and ε-lactones were similarly disappointing in this regard.



20 **21** **22** **23**

Table 1: On the Lewis acid mediated union of *N*-methylpyrrole with β-butyrolactone

Conditions	20	21	22	23
5eq. $AlCl_3$, $CHCl_3$, 60°C	21%	24%	-	5%
5eq. $TiCl_4$, $CHCl_3$, 20°C	21%	24%	13%	14%
5eq. $TiCl_4$, $CHCl_3$, -20°C	3%	45%	5%	45%

At this time we are uncertain why arenes should undergo alkylation with lactones while pyrroles provide the products of acylation. It is our assumption that electronic factors play a critical role. Current effort is aimed at further delineating the scope of this methodology and exploiting the annulation sequence in target oriented synthesis.[6]

Acknowledgements: The authors wish to thank The University of Southampton for their financial support (to RFD), Mrs. Joan Street for the n.O.e. studies and the EPSRC mass spectrometry service.

References

1. a. Eijkmann, J.F. *Chem. Weekblad*, 1904, *1*, 421; b. Eijkmann, J.F. *Chem. Zentr.*, 1904, *75*, 1416.
2. a. Beyer, H. *Ber.*, 1937, *70*, 1101; b. Christian, R.V., Jr. *J. Am. Chem. Soc.*, 1952, *74*, 1591; c. Schuster, D.I.; Curran, W.V. *J. Org. Chem.*, 1970, *35*, 4192; d. Huffman, J.W.; Starnes, J.J. *J. Org. Chem.*, 1972, *37*, 487; e. Din, L.B.; Meth-Cohn, O.; Walshe, N.D.A. *J. Chem. Soc., Perkin Trans. 1*, 1991, 781 and f. Shaver, F.W. *US Patent* 2,587,540, 1952: *Chem. Abs.*, 1952, *46*, 9603c.
3. a. Mosby, W.L. *J. Am. Chem. Soc.*, 1952, *74*, 2564 and b. Yuste, F.; Walls, F. *Aust. J. Chem.*, 1976, *29*, 2333.

4. **a.** Quallich, G.; Williams, M.; Friedmann, R.C. *J. Org. Chem.*, **1990**, *55*, 4971 and **b.** Bruce, D.B.; Sorrie, A.J.S.; Thomson, R.H. *J. Chem. Soc.*, **1953**, 2403.
5. For the direct alkylation of indoles and pyrroles with β-lactones see: **a.** Harley-Mason, J. *J. Chem. Soc.*, **1952**, 2433 and **b.** Harley-Mason, J. *Chem. and Ind.*, **1951**, 886. For an intramolecular *alkylation* of a pyrrole with a γ-lactone see: **c.** Ratcliffe, A.H.; Smith, G.F.; Smith, G.N. *Tetrahedron Lett.*, **1973**, 5179.
6. Harrowven, D.C.; Dennison, S.T.; Howes, P. *Tetrahedron Lett.*, **1994**, *35*, 4243.
7. **a.** Olah, G.A.; Krishnamurti, R.; Prakash, G.K.S. Friedel-Crafts Alkylations. In *Comprehensive Organic Synthesis*, Trost, B.M. Ed.; Pergammon: Oxford, Vol. 3, 1991, pp 293; **b.** Heaney H. The Bimolecular Aromatic Friedel-Crafts Reaction. In *Comprehensive Organic Synthesis*, Trost, B.M. Ed.; Pergammon: Oxford, Vol. 3, 1991, pp 733 and **c.** Heaney H. The Intramolecular Aromatic Friedel-Crafts Reaction. In *Comprehensive Organic Synthesis*, Trost, B.M. Ed.; Pergammon: Oxford, Vol. 2, 1991, pp 753.
8. We use this reaction to illustrate a typical experimental proceedure. To a stirred solution of γ-butyrolactone (200mg, 2.3mmol) and *N*-methylpyrrole (940mg, 11.6mmol) in chloroform (5ml) at ambient temperature under nitrogen was added aluminium trichloride (1.55g, 11.6mmol). The reaction darkened appreciably. It was heated to 60°C for 3h, then cooled and partitioned between dichloromethane (200ml) and 2M HCl (200ml). The organic extract was washed with brine (80 ml), dried over magnesium sulfate, concentrated and purified by column chromatography (silica, gradient elution, 10% to 50% ether in petroleum ether) to give firstly the tetrahydroindolone **5** (30mg, 0.20mmol, 9%) then the ketone **2** (308mg, 1.8mmol, 80%) and finally the tetrahydroindolone **4** (28mg, 0.19mmol, 8%).
9. All products gave satisfactory analytical and spectroscopic characteristics *e.g.* **2** colourless oil; UV (EtOH) λ_{max} (ε) 287 (11,000) and 254sh (4,200) nm; **FT-IR** (thin film) υ_{max} 3400brs, 2945m, 2860m, 1645s, 1530m, 1410s, 1060s and 740s cm^{-1}; ^1H NMR (250MHz, $CDCl_3$), δ_H 7.01 (1H, dd, *J*=4.1, 1.6Hz), 6.82 (1H, dd, *J*=2.5, 1.6Hz), 6.13 (1H, dd, *J*=4.1, 2.5Hz), 3.94 (3H, s), 3.72 (2H, t, *J*=6.1Hz), 2.95 (2H, t, *J*= 7.0Hz), 2.55 (1H, brs) and 1.96 (2H, app. quin, *J*=6.5Hz) ppm; ^{13}C NMR (75MHz, $CDCl_3$) δ_C 191.5 (s), 131.2 (d), 130.5 (s), 119.5 (d), 108.0 (d), 62.4 (t), 37.7 (q), 35.9 (t) and 27.7 (t) ppm; $^m/_z$ (EI) 167 ($[M]^+$, 10%), 149 (22), 123 (40), 108 (100) and 80 (18) amu; (CI) found 167.0946, $C_9H_{13}NO_2$ requires 167.0946; and **12** colourless oil; UV (EtOH) λ_{max} (ε) 286 (5,500) nm; **FT-IR** (thin film) υ_{max} 2930m, 1645s, 1510m, 1430m, 1405m and 1000m cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ_H 6.75 (1H, d, *J*=2.2Hz), 6.01 (1H, d, *J*=2.2Hz), 3.90 (3H, s), 2.91 (1H, dqd, *J*=11.1, 7.0, 4.4Hz), 2.55 (1H, ddd, *J*=16.6, 10.6, 4.4Hz), 2.46 (1H, ddd, *J*=16.6, 5.5, 4.4Hz), 2.12 (1H, app.dq, *J*=13.2Hz, 4.4Hz), 1.73 (1H, app.dtd, *J*=13.2, 11.1, 5.5Hz) and 1.30 (3H, d, *J*=7.0Hz) ppm; **n.O.e** (360MHz, $CDCl_3$) irradiation of the signal at δ 6.75 caused an n.O.e. enhancement at δ 1.30 ($CHCH_3$) while irradiation of the signal at δ 6.01 caused an n.O.e. enhancement at δ 3.90 (NCH_3); ^{13}C NMR (75MHz, $CDCl_3$) δ_C 189.1 (s), 142.9 (s), 130.4 (d), 126.4 (s), 105.4 (d), 38.5 (t), 36.4 (q), 33.7 (t), 29.6 (d) and 20.1 (q) ppm; $^m/_z$ (EI) 163 ($[M]^+$, 70%), 148 (73), 134 (13), 120 (100) and 106 (28) amu. With one exception, yields refer to pure, isolated samples and were calculated with respect to the lactone (we were unable to effect separation of the isomeric carboxylic acids **21** and **23**; ^1H NMR integration of the NCH_3 signal and aromatic protons being used to determine the yield of each product).
10. Kakushima, M.; Hamal, P.; Frenette, R.; Rokach, J. *J. Org. Chem.*, **1983**, *48*, 3214.
11. **a.** Arnold, R.T.; Buckley, J.S.; Richter, J. *J. Am. Chem. Soc.*, **1947**, *69*, 2322. **b.** Truce, W.E.; Olson, C.E. *J. Am. Chem. Soc.*, **1952**, *74*, 4721. **c.** Yuste, F.; Walls, F. *Aust. J. Chem.*, **1976**, *29*, 2333; **d.** Williams, M.; Quallich, G. *Chem. Ind. (London)*, **1990**, 315 and references 4a and 6.
12. Brauman, J.I.; Pandell, A.J. *J. Am. Chem. Soc.*, **1967**, *89*, 5421.
13. Rinehart, K.L., Jr.; Gustafson, D.H. *J. Org. Chem.*, **1960**, *25*, 1836.

(*Received in UK* 3 *May* 1995; *revised* 10 *July* 1995; *accepted* 14 *July* 1995)