

## Synthesis of Some Aryl $\alpha$ -Diketones and Aryl Glyoxylic Acid Derivatives by Acylation of Electron-rich Aromatics

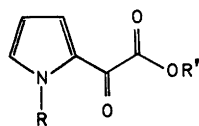
DAN BEHR, SVANTE BRANDÅNGE and BJÖRN LINDSTRÖM

*Department of Organic Chemistry, The Arrhenius Laboratory,  
P.O.B., S-104 05 Stockholm 50, Sweden*

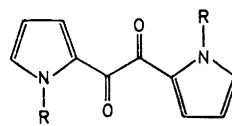
*N*-Acyropyridinium salts, prepared from pyridine and oxalyl chloride or ethoxalyl chloride, have been used for acylation of electron-rich aromatics of the pyrrole, indole, and furan groups.

Acylation of electron-rich heteroaromatics is sometimes complicated by the acid-sensitivity of the starting aromatic. Some reactions, without a catalyst, between oxalyl chloride and aromatics such as indole,<sup>1,2</sup> pyrrole,<sup>3-5</sup> *N*-methylpyrrole,<sup>3</sup> and 2,4-dimethylpyrrole<sup>6</sup> have been performed with varying degrees of success.

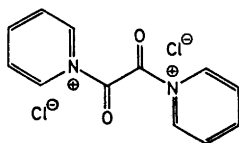
Treibs and Kreuzer<sup>3</sup> used the *N*-acylammonium salt obtained on reaction between oxalyl chloride and triethylamine (1:1) for acylation of *N*-methylpyrrole. After quenching with methanol, methyl *N*-methyl-2-pyrrolylgy-



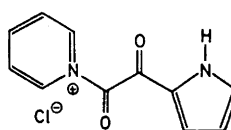
I R = CH<sub>3</sub>, R' = CH<sub>3</sub>  
III R = H, R' = C<sub>2</sub>H<sub>5</sub>



II R = CH<sub>3</sub>  
IV R = H



V



VI

oxylate (I) and bis(*N*-methyl-2-pyrrolyl)-ethanedione (II) were obtained in moderate yields (30 and 37 %, respectively). We have reported a similar acylation reaction.<sup>7</sup> Ethyl 2-pyrrolylgyoxylate (III) was obtained in 64 % isolated yield from the reaction between pyrrole, pyridine, and ethoxalyl chloride at  $-80^{\circ}$  for 3 h. We now report further studies on this and related acylations.

When the above reaction was carried out at  $-70^{\circ}$  for 17 h, the yield of III, determined by GLC, was 96 %. Lower yields (75 and 70 %, respectively) were obtained when the temperature was allowed to rise from  $-70^{\circ}$  to room temperature or when the reagents were kept at room temperature throughout. Ethyl 3-indolylgyoxylate was prepared (92 % yield) in an analogous reaction.

When equimolar amounts of pyridine, oxalyl chloride, and pyrrole were used, and the reaction was quenched with ethanol, III was also obtained. Ethyl 3,5-dimethyl-4-ethoxycarbonyl-2-pyrrolylgyoxylate was prepared in an analogous reaction. When, however, pyridine, oxalyl chloride, and pyrrole were used in the molar proportions 2:1:1, different results were obtained depending upon the dilution of the reaction mixture. At high concentrations, when the mixture was heterogeneous, bis(2-pyrrolyl)-ethanedione (IV) was the main product (53 % yield), and the ketoester III was formed in low yield (<4 %). In dilute homogeneous solution, III was obtained in 60 % yield. The yield of III raised to 92 % when the bis-pyridinium salt was used in excess. A reasonable explanation of this difference in result is that at higher concentrations the major part of the bis-pyridinium salt V is precipitated and the mono-pyridinium salt VI becomes the main acylating agent. In dilute solutions, however, all V is in solution and this compound then becomes the main acylating agent. The presence of a bis-pyridinium salt was demonstrated by mixing oxalyl chloride (0.010 mol) with pyridine (0.022 mol) in methylene chloride at  $-70^{\circ}$ , followed by filtration and determination of the amount of pyridine in the mother liquor.

The less reactive 2-methylfuran, on reaction with equimolar amounts of pyridine and oxalyl chloride and quenching with methanol, gave the corresponding methyl glyoxylate in good yield (77 %). Poor yields were, however, obtained with the even less reactive furan and 2-methylthiophene.

$\alpha$ -Diketones were also prepared from *N*-methylindole and 2-methylfuran by reacting the aromatic, oxalyl chloride, and pyridine in the molar proportions 2:1:2.

#### EXPERIMENTAL

Analytical GLC was performed using a 3 % JXR on Gas-Chrom Q column (0.2  $\times$  180 cm) mounted in a Perkin-Elmer 900 chromatograph. Melting points are corrected. IR spectra were recorded with a Perkin-Elmer 257 instrument. Methylene chloride was distilled over  $P_2O_5$ , and pyridine was distilled over KOH and stored over molecular sieves (3 Å).

*Ethyl 2-pyrrolylgyoxylate*<sup>7</sup> (III). A solution of pyridine (0.95 g, 12 mmol) in methylene chloride (25 ml) and thereafter a solution of pyrrole (0.67 g, 10 mmol) in methylene chloride (25 ml) were slowly added (15 min for each) to a stirred and cooled ( $-70^{\circ}$  to  $-80^{\circ}$ ) solution of ethoxalyl chloride (1.50 g, 11 mmol) in methylene chloride (25 ml). The reaction mixture was stirred for 17 h ( $-70^{\circ}$ ) and washed with dilute hydrochloric acid, and the organic layer was then dried ( $Na_2SO_4$ ). Quantitative GLC analysis (internal standard) revealed that III was formed in 96 % yield.

*Ethyl 3-indolylglyoxylate (VII)*. A solution of pyridine (2.85 g, 0.036 mol) in methylene chloride (50 ml) and thereafter a solution of indole (3.51 g, 0.030 mol) in methylene chloride (100 ml) were added to a stirred and cooled ( $-80^{\circ}$ ) solution of ethoxalyl chloride (4.50 g, 0.033 mol) in methylene chloride (100 ml). The cooling bath was then removed and the mixture was stirred for 20 h. Crystals of VII were filtered off (3.71 g, m.p.  $185-186.5^{\circ}$ , lit.<sup>8</sup> m.p.  $187^{\circ}$ ), and a second crop (2.28 g, m.p.  $185-186.5^{\circ}$ ) was obtained from the mother liquor. The total yield was 5.99 g (92 %).

*Ethyl 2-pyrrolylgyoxylate (III)*. A solution of pyridine (2.61 g, 33 mmol) in methylene chloride (50 ml) and thereafter a solution of pyrrole (2.01 g, 30 mmol) in methylene chloride (50 ml) were added to a stirred and cooled ( $-80^{\circ}$ ) solution of oxalyl chloride (4.19 g, 33 mmol). The reaction mixture was stored at  $-20^{\circ}$  for 18 h and ethanol (4.6 g) was then added. After 3 h at room temperature the mixture was washed with dilute hydrochloric acid, and the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography on silica gel (methylene chloride) yielded pure III (4.17 g, 83 % yield), indistinguishable (IR, NMR, GLC) from an otherwise prepared<sup>7</sup> sample.

*Ethyl 3,5-dimethyl-4-ethoxycarbonyl-2-pyrrolylgyoxylate (VIII)*. The reaction between 2,4-dimethyl-3-ethoxycarbonylpyrrole<sup>9</sup> (167 mg, 1.0 mmol), oxalyl chloride (141 mg, 1.1 mmol), and pyridine (95 mg, 1.2 mmol) in methylene chloride (10 ml) was started at  $-80^{\circ}$  and was then allowed to reach room temperature. Ethanol was added after 1 h, and the reaction mixture was worked up as above. Purification on silica gel (chloroform) gave 245 mg of VIII (92 % yield, m.p.  $74-76^{\circ}$ , lit.<sup>8</sup> m.p.  $80^{\circ}$ ).

*Bis(2-pyrrolyl)-ethanedione (IV)*. A solution of pyridine (10.0 g, 0.12 mol) in methylene chloride (25 ml) and thereafter a solution of pyrrole (3.3 g, 0.050 mol) in methylene chloride (25 ml), were added with stirring to a cooled ( $-80^{\circ}$ ) solution of oxalyl chloride (6.4 g, 0.050 mol) in methylene chloride (25 ml). After 15 min the mixture was washed with dilute hydrochloric acid, and the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification on a silica gel column (acetone) gave IV as yellow crystals (2.5 g, 53 %, m.p.  $203-205^{\circ}$ , lit.<sup>10</sup> m.p.  $199-200^{\circ}$ ).

*Ethyl 2-pyrrolylgyoxylate (III)*. Oxalyl chloride (0.64 g, 5.0 mmol), pyridine (1.0 g, 12 mmol) and methylene chloride (450 ml) were mixed at  $-80^{\circ}$ , and when warmed to  $-10^{\circ}$  the mixture became homogeneous. A solution of pyrrole (0.165 g, 2.5 mmol) in methylene chloride was then added dropwise, and after 10 min ethanol (10 ml) was added. Part of the solvent was evaporated and the resulting solution was washed with dilute hydrochloric acid. After drying ( $\text{Na}_2\text{SO}_4$ ) and concentration of the organic layer a blue crystalline mass was obtained. NMR showed that this consisted of reasonably pure III (92 % yield).

*Methyl 5-methylfurylgyoxylate (IX)*. A solution of pyridine (4.35 g, 55 mmol) in methylene chloride (50 ml) and thereafter a solution of 2-methylfuran (4.11 g, 50 mmol) were added dropwise with stirring and cooling ( $-80^{\circ}$ ) to a solution of oxalyl chloride (7.61 g, 60 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 18 h. After reaction with methanol and the usual work-up a brown oil (8.8 g) was obtained. Purification on silica gel (methylene chloride) gave IX as yellow needles (6.50 g, 77 % yield), m.p.  $56-57^{\circ}$ . An analytical sample, m.p.  $56-57^{\circ}$ , was obtained on recrystallisation from light petroleum. (Found: C 57.4; H 4.94. Calc. for  $\text{C}_8\text{H}_8\text{O}_4$ : C 57.1; H 4.80.) IR ( $\text{CHCl}_3$ ): 1740 and  $1662\text{ cm}^{-1}$ .

*Bis(5-methyl-2-furyl)-ethanedione (X)*. A solution of pyridine (6.96 g, 88 mmol) in methylene chloride (50 ml) and thereafter a solution of 2-methylfuran (6.57 g, 80 mmol) in methylene chloride (50 ml) were added dropwise with stirring to a solution of oxalyl chloride (5.08 g, 40 mmol) in methylene chloride (50 ml) at  $-70^{\circ}$ . The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h. A dark brown residue was obtained after extraction with hydrochloric acid, drying ( $\text{Na}_2\text{SO}_4$ ) and concentration of the organic layer. Purification on a silica gel column (methylene chloride) gave X as yellow crystals (4.41 g, 51 % yield, m.p.  $166.5-167^{\circ}$ ). An analytical sample, m.p.  $166.5-167^{\circ}$ , was obtained from ethanol. (Found: C 65.9; H 4.81. Calc. for  $\text{C}_{12}\text{H}_{10}\text{O}_4$ : C 66.1; H 4.62.) IR ( $\text{CHCl}_3$ ):  $1642\text{ cm}^{-1}$ .

*Bis(N-methyl-3-indolyl)-ethanedione (XI)*. Methylene chloride solutions (50 ml) of oxalyl chloride (0.65 g, 5.1 mmol), pyridine (0.95 g, 12 mmol) and *N*-methylindole (1.31 g, 10 mmol) were mixed at  $-70^{\circ}$ , and the mixture was stirred at room temperature (18 h) producing an orange colour. After washing with dilute hydrochloric acid, drying and

concentration, the residue was crystallised from benzene giving pale yellow crystals, m.p. 272–273.5° (0.70 g, 45 %, lit.<sup>8</sup> m.p. 268–269°).

*Acknowledgement.* This work has been supported by the *Hierta-Retzius' forskningsfond*.

## REFERENCES

1. Giua, M. *Gazz. Chim. Ital.* **54** (1924) 593.
2. Shaw, K., McMillan, A., Gudmundson, A. and Armstrong, M. *J. Org. Chem.* **23** (1958) 1171.
3. Treibs, A. and Kreuzer, F.-H. *Ann.* **721** (1969) 105.
4. Archibald, J. L. and Freed, M. E. *J. Heterocycl. Chem.* **4** (1967) 335.
5. Birchall, G. R. and Rees, A. H. *Can. J. Chem.* **49** (1971) 919.
6. Nenitzescu, C. D., Necsoin, I. and Zalman, M. *Comun. Acad. Rep. Populare Romine* **8** (1958) 659; *Chem. Abstr.* **53** (1959) 17092.
7. Brandänge, S. and Lundin, C. *Acta Chem. Scand.* **25** (1971) 2447.
8. Millich, F. and Becker, E. I. *J. Org. Chem.* **23** (1958) 1096.
9. Knorr, L. *Ann.* **236** (1886) 325.
10. Oddo, B. *Gazz. Chim. Ital.* **41** (1911) 248.

Received March 3, 1973.