Tetrahedron, 1966, Vol. 22, pp. 2003 to 2006. Pergamon Press Ltd. Printed in Northern Ireland

LOW-TEMPERATURE ACETOACETYLATION OF WEAKLY NUCLEOPHILIC COMPOUNDS

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(*Received* 31 *December* 1965)

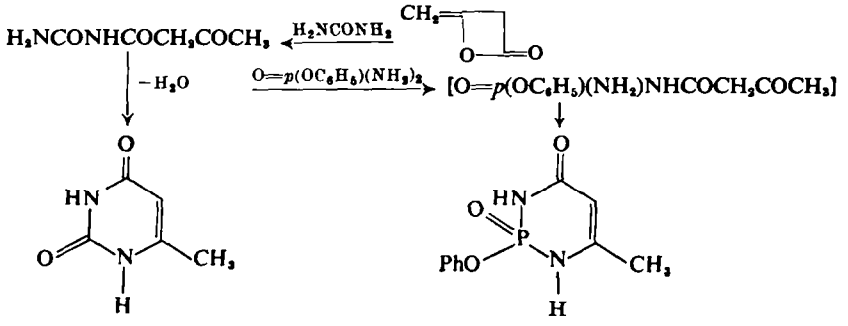
Abstract—Mercuric salts can be used as effective catalysts for the acetoacetylation of weakly nucleophilic compounds with diketene in acetic acid solution at room temperature.

DIKETENE is widely used as acetoacetylating agent for the preparation of acetoacetic acid derivatives, unsaturated ketones and heterocyclic compounds.[1–5] Diketene is known to react readily with simple alcohols, amines and mercaptans, but the acetoacetylation of ureas, aromatic amines and other weak nucleophiles usually proceeds at elevated temperatures even in the presence of catalysts such as pyridine.[6–10]

It has recently been shown that mercuric salts accelerate the reactions of diketene with urea, *p*-nitroaniline and diphenylamine in acetic acid solution at room temperature.[11,12] Further work on the low-temperature acetoacetylation of various nucleophilic reagents is reported in this paper. It has been found that the inorganic Hg-salts possess the high catalytic activity but, in some cases, $Hg(OOCCH_3)_2$ provides a more unambiguous course of the acetoacetylation (Exp. 5, Table 1).

It is interesting that BF_3, H_2SO_4, $ZnCl_2$, $AlCl_3$, $Cu(OOCCH_3)_2$, $FeCl_3$, H_2PtCl_6 and $(CH_3)_2Hg$ have no appreciable effect on the behaviour of diketene towards urea in acetic acid solution at room temperature (~3 hr).

The $HgSO_4$-catalysed acetoacetylation of urea and phosphorodiamidic acid phenyl ester is accompanied by cyclization of the intermediate β-dicarbonyl compounds to produce the corresponding heterocycles.



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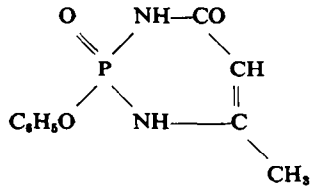
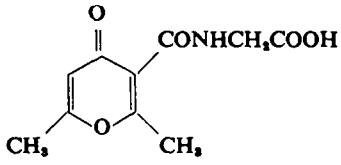
[12] V. I. Gunar, L. F. Ovechkina, I. A. Mikhailopulo, S. I. Zavialov, USSR Patent, 936526/23-4 (1965).

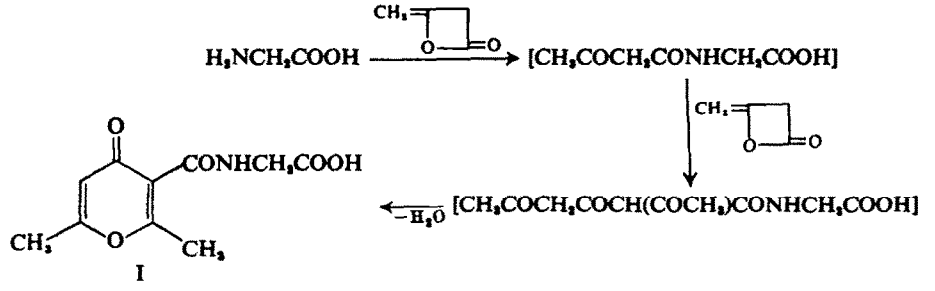
TABLE 1. MERCURIC SALT-CATALYSED ACETOACETYLATION OF WEAKLY NUCLEOPHILIC REAGENTS WITH DIKETENE IN ACETIC ACID SOLUTION

Exp. number	Starting compound	Reaction time, hr	Reaction product	m.p.s.	Yield %
1	Urea	3	acetoacetic acid ureide[11]	142–144°	79
2	Urea	3	6-methyluracil[11]	308–310° (from H_2O)	61
3	Phenylurea	3	acetoacetic acid 1-phenylureide[11]	144–145°	55
4	Phosphoro-diamidic acid phenyl ester	3		220–221°	68
5	Urethan	36	acetoacetylurethan	72–74° (from heptane-benzene)	44
6	*p*-Nitroaniline	0·5	acetoacetic acid p-nitroanilide[13]	119–121°	85
7	Diphenylamine	24	acetoacetic acid diphenylamide	75–77°	95
8	Glycine	72		225–227° (from H_2O)	18
9	Phenol	20	phenyl acetoacetate[14]	49–50° (from heptane —$CHCl_3$)	64
10	β-Naphtol	20	β-naphtylacetoacetate[14]	81–82°	92

[13] L. Monti, V. Cirelli, *Gazz. Chim. Ital.* **66**, 723 (1936).
[14] R. N. Lacey, *J. Chem. Soc.* 854 (1954).

The use of $Hg(OOCCH_3)_2$ as catalyst permits the reaction of diketene with urea to be stopped at the open-ureide stage.

The reaction between diketene and glycine involves a diacetoacetylation process leading to a γ-pyrone (I):



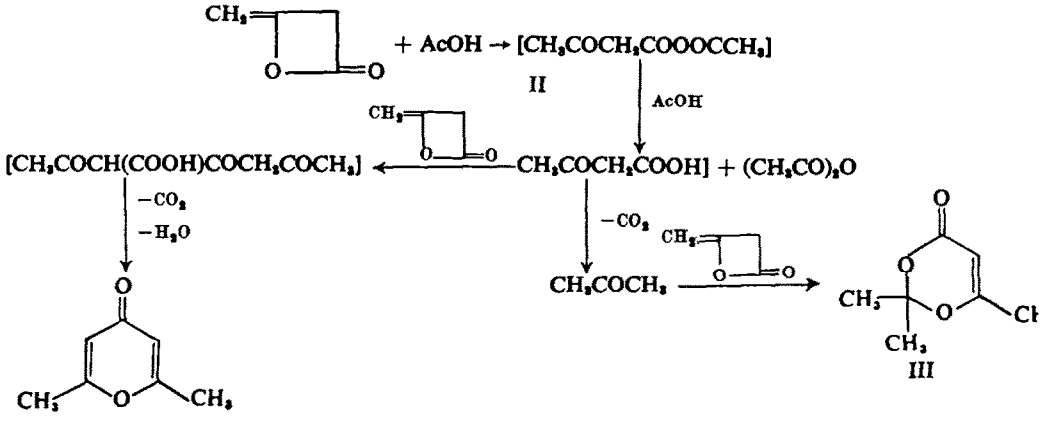
I

A similar transformation has been observed on treatment of diketene with phenylurea or thiourea in pyridine solution.[4]

The catalytic activity of mercuric salts could be due to the intermediate formation of a co-ordination complex with an active electrophilic centre on the carbonyl carbon atom.

A mixed anhydride (II)[15] derived from diketene and acetic acid may also exhibit acetoacetylating properties. This is in agreement with the fact that mercuric salts are able to catalyse the decomposition of diketene in acetic acid at room temperature to give a mixture of acetone, acetic anhydride, 2,6-dimethylpyrone and 2,2,4-trimethyl-6-oxo-1,3-dioxene (III).

These transformations may be represented as proceeding through the mixed-anhydride (II) stage according to the following scheme:



III

EXPERIMENTAL

Mercuric salt-catalysed acetoacetylation of weak nucleophiles in acetic acid solution. Diketene (1·2 mole; 6 moles in Exp. 8) was slowly added to a solution or a suspension of a nucleophilic reagent (1 mole) and $Hg(OOCCH_3)_2$ (0·02–0·1 mole) (Exps 1, 3, 5, 7–10 in Table 1) or $HgSO_4$ (0·02–0·1 mole) (Exps 2, 4, 6) in glacial AcOH. After completion of the exothermic reaction, the mixture was allowed to stand at room temp for several hr. The acetoacetylation products were isolated in the

[15] H. J. Hagemeyer, US Patent 2476859; *Chem. Abstr.* **43**, 8398 (1949).

following manner: by dilution with ether (Exps 1, 3) or water (Exps 6, 7); by evaporation and treatment of the residue with water (Exps 2, 4, 8, 10) or ether at −70° (Exps 5, 9).

Under the same conditions, but without catalysts, the acetoacetylation reactions proceed very slowly (Exps 1–5, 8, 9, 10) or give impure products (Exps 6, 7).

Reaction of diketene with urea. Diketene (3 ml) was added to a suspension of urea (1·5 g) and $HgSO_4$ (0·19 g) in glacial AcOH (5 ml). The reaction was very exothermic and the temp rose to 100–110°. The reaction mixture was kept at room temp for 2.5–3 hr and then diluted with water. After standing at room temp for 12 hr the precipitate was filtered off to give 2·2 g of 6-methyluracil, m.p. and mixed m.p. 308–310°.

Reaction of diketene with phosphorodiamidic acid phenyl ester. Diketene (2 ml) was added to a solution of $HgSO_4$ (0·2 g) and phosphorodiamidic acid phenyl ester (1·72 g) in glacial AcOH (10 ml). When no longer exothermic, the mixture was allowed to stand at room temp for 1.5–2 hr and then evaporated *in vacuo* to dryness. The residue was treated with water and the precipitate was filtered off to give 1·6 g of 2-phenoxy-2-oxo-2-phospho-6-methyluracil, m.p. 215–217°.

The product was purified by dissolving in aqueous acetone passing through silica gel, evaporating *in vacuo* to dryness and washing the residue with water, acetone and ether, m.p. 220–221°. It gives no colour reaction with $FeCl_3$. (Found: C, 50·0; H, 4·4; N, 11·9; P, 12·8. $C_{10}H_{11}N_2PO_5$ requires C, 50·4; H, 4·4; N, 11·8; P, 13·0%.) λ_{max}^{EtOH} 260 mμ (ε 8160). IR_{KBr}: maxima (cm^{-1}) at 3420, 3120, 3065, 1665, 1642, 1490, 1470, 1260, 1235, 1180.

Reaction of diketene with glycine. Diketene (12 ml) was slowly added to a suspension of $Hg(OOCCH_3)_2$ (0·2 g) and glycine (3 g) in glacial AcOH. After the completion of the exothermic reaction, the mixture was left standing at room temp for 36 hr and then concentrated *in vacuo* to dryness. The residue was washed with water and MeOH to give 1·6 g of 2,6-dimethylpyronecarboxylic acid N-carboxymethylamide, m.p. 225–227° (from H_2O). It gives no enol colour reaction with $FeCl_3$. (Found: C, 53·3; H, 5·1. $C_{10}H_{11}O_5N$, requires: C, 53·3; H, 4·9%.) λ_{max}^{EtOH} 233, 266 mμ (ε 22,500, 13,600). IR_{KBr} maxima (cm^{-1}) at 3440, 1685, 1635, 1520, 1460, 1375, 1290, 1250.

Methyl ester, m.p. 135–137° (from dipropylic ether). (Found: C, 55·4; H, 5·7; N, 5·8. $C_{11}H_{13}O_5N$ requires: C, 55·2; H, 5·5; N, 5·8%.) λ_{max}^{EtOH} 230, 262 mμ (ε 20,600, 12,600).

Mercuric salt-catalysed decomposition of diketene in acetic acid solution. A mixture of diketene (15 ml), $Hg(OOCCH_3)_2$ (0·2 g) and glacial AcOH (15 ml) was kept at room temp for 72 hr and then submitted to distillation under atm. press. 16 g of a fraction (b.p. under 145°) was collected which contained acetone, AcOH and its anhydride, as shown by VPC. The residue was treated with ether, the precipitate (3,4 g; m.p. 105–110°) was filtered off and chromatographed on alumina grade II. Elution with $CHCl_3$ gave 1·7 g of 2,6-dimethylpyrone (m.p. and mixed m.p. 130–132°). The mother liquor was distilled *in vacuo* and a fraction, b.p. 60–120°/7 mm, was chromatographed on alumina grade II. Elution with ether and $CHCl_3$ gave respectively 0·4 g of 2,2,4-trimethyl-6-oxo-1,3-dioxene, b.p. 82–83°/7 mm, n_D^{20} 1·4630, λ_{max}^{EtOH} 248 mμ (ε 5530) (reported[16]) b.p. 65–67°/2 mm, n_D^{20} 1·4636, λ_{max}^{EtOH} 247·5 mμ (1 g ε 3·92) and additional 1·4 g of 2,6-dimethylpyrone, m.p. 130–131°.

The same products were obtained by carrying out the decomposition of diketene in the presence of $HgSO_4$, but in this case the reaction was much more exothermic.

Acknowledgement—The authors wish to thank I. S. Runge and B. V. Lopatin for spectroscopic investigations.

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