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UREA AS A BASE IN ORGANIC REACTIONS+

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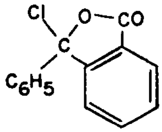
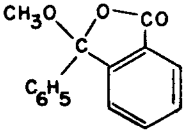
In this paper, the effectiveness of urea as a base for the neutralization of strong acids in alcoholic solution is emphasized. This property is important because there should be many cases of reactions involving acid halides in which urea is capable of replacing the more expensive and malodorous pyridine bases commonly used.

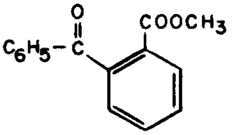
When 3-chloro-3-phenylphthalide (I)[1] is allowed to react with methanol in the cold, esterification is essentially complete in one min. The initial product is almost entirely the ψ- methyl ester (II). If this solution is allowed to stand in the presence of the hydrogen chloride produced, the methanol present reacts rapidly by addition to the carbonyl group of II to yield the normal methyl ester (III). For example, II is 39% converted to III in 15 minutes in 0.2 N. methanolic HCl[2] at 55°. In order to prevent the reaction of II with methanol, aqueous sodium carbonate[3] and pyridine[4] have been used.



I



II



III

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Many years ago[†] we used urea instead of pyridine in carrying out this esterification[5]. In general, if the reaction is carried out in the cold, over 90% yields of II (containing 2-10% of III) are obtained when urea, pyridine or other tertiary amines are present. We believe that the small amounts of III produced are formed by reaction of methanol by addition to the carbonyl group of I and not by isomerization of II to III in the reaction mixture because II does not isomerize to III in methanol containing urea or the tertiary amines and strong acids. When tetramethylurea[‡] is used in place of urea the conversion of II to III in acidic methanol takes place to a small extent. Thus, tetramethylurea is not as effective as urea or tertiary amines but it does have an effect. Since tetramethylurea is much more soluble than urea in many organic solvents, it may prove a desirable reagent in certain cases.

Thus there seems to be no reason to doubt that in many other reactions, urea and alkylated ureas will prove effective as bases when neutralization of strong acids is required[6].

ψ-Methyl *O*-Benzoylbenzoate (II)--An ice cold solution of 0.075 mole of pyridine (or other base such as urea) in 30 ml. of dry methanol was added all at once to a swirled solution of 0.05 mole of I in a small amount of dry ether (or to solid I) at 0°. After 1 min. the solvents were rapidly removed on a rotary evaporator under reduced pressure. An ether solution of the residue was washed with solutions of dilute acid, dilute Na_2CO_3, saturated NaCl, and then filtered through anhydrous magnesium sulfate. After removal of solvent the residue was subjected to n.m.r. analysis in $CDCl_3$ with TMS as internal standard (II has a singlet at 3.21 ppm, III at 3.59).[7] In reactions in which urea and collidine were used no III was observed. In reactions involving pyridine, N-methylpiperidine and triethylamine from 3-10% of III was present, as was the case when no base at all or a small amount of water was used. The yield of ester was about 90% in all cases, the remainder being *O*-benzoylbenzoic acid.

Conversion of II to III--In a typical experiment without added base, a solution of 0.001 mole of II in 5 ml. of pure methanol was added to a solution of 0.001 mole of *p*-toluenesulfonic acid (or HCl) in 10 ml. of methanol at room temperature and the solution allowed to stand for

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[†] I cannot remember when we first used urea in this reaction or why it was tried. M. S. Newman

[‡] We are indebted to Dr. John Reynard, DuPont Company for a generous sample of tetramethylurea.

2 hrs. After treatment with excess Na_2CO_3 the ester was isolated and shown to consist of 45-50% of III (CH_3 singlet at 3.59 ppm)[7] and the remainder II (CH_3 singlet at 3.21 ppm)[7] by n.m.r. analysis. When 0.002 mole of pyridine, or urea, was added to the acid methanolic solution several min. prior to the addition of II, the ester recovered was entirely unchanged II. In similar experiments in which 0.002 mole of tetramethylurea was used, mixtures of about 15% of III and 85% of II were obtained.

Esterification of *tert*-Butyl Alcohol--In a typical experiment, a solution of 0.1 mole of acetyl chloride was added dropwise to a cooled solution of 0.1 mole *tert*-butyl alcohol in 25-30 ml. of dry ether. The mixture spontaneously warmed to reflux and was maintained at reflux for 1 hr. The ester formed was isolated by conventional means and the *tert*-butyl acetate, b.p. 92-95°, was collected with the aid of a small still. The yield varied from 15 to 20% on the average.

When similar experiments were run except that 0.15 mole of urea, tetramethylurea or pyridine was present in the ether solution, yields of 50-60% of ester were obtained. In experiments involving 0.15 mole of N,N-dimethylacetamide the ester yield was 30-35%.

REFERENCES

1. The acid chloride of O-benzoylbenzoic acid is entirely in the cyclic form (I) however made, M. S. Newman and C. Courduvelis, J. Am. Chem. Soc., 88, 781 (1966).
2. M. S. Newman and C. Courduvelis, J. Org. Chem., 30, 1795 (1965).
3. H. Meyer, Monatsh., 25, 475 (1904).
4. M. S. Newman and C. D. McCleary, J. Am. Chem. Soc., 63, 1537 (1941).
5. The equilibrium constant for the reaction, $H_2NCONH_3^+ + CH_3OH \rightleftarrows H_2NCONH_2 + CH_3OH_2^+$ is 4.37 ±0.2 x 10^{-4} moles/l. R. G. Pearson and J. Tucker, J. Am. Chem. Soc., 71, 749 (1949).
6. The use of urea as a base in solvolysis reactions has been reported by W. S. Trahanovsky, M. P. Doyle and P. D. Bartlett, J. Org. Chem., 32, 150 (1967).
7. P. T. Lansbury and J. F. Bieron, J. Org. Chem., 28, 3564 (1963).