- 1. A. N. KOST and I. J. GRANDBERG. In Advances in heterocyclic chemistry. Vol. 6. Edited by A. R. Katritzky and A. J. Boulton. Academic Press, Inc., New York. 1966. p. 381.
- W. E. PARHAM and J. L. BLEASDALE. J. Am. Chem. 2. Soc. 73, 4664 (1951).
- D. E. McGreer and W.-S. Wu. Can. J. Chem. 45, 3. 461 (1967), and earlier papers.
- K. D. GUNDERMANN and R. THOMAS. Chem. Ber. 4. 93, 883 (1960).
- D. E. MCGREER, W. WAI, and G. CARMICHAEL. Can. J. Chem. 38, 2410 (1960). 5
- 6. H. BEYER and G. WOLTER. Chem. Ber. 89, 1652 (1956).
- S. INAYAMA and M. YANAGITA. J. Org. Chem. 27, 1465 (1962).
- 8. P. J. KROPP. Tetrahedron Letters, 3647 (1964).
- 9. P. BIEBER. Ann. Chem. 9, 674 (1954).
 10. M. C. FORD and W. A. WATERS. J. Chem. Soc. 1851 (1951).
- 11. C. RAPPE and K. ANDERSON. Acta Chem. Scand. 21, 1741 (1967).
- 12. J. E. BLACKWOOD, C. L. GLADYS, K. L. LOENING, A. E. PETRARCA, and J. E. RUSH. J. Am. Chem. Soc. 90, 509 (1968).

Convenient new synthesis of 1,3-diaroylureas¹

NOTES

JAMES F. WOLFE AND GEORGE B. TRIMITSIS Department of Chemistry, Virginia Polytechnic Institute, Blacksburg, Virginia 24061

Received January 14, 1969

It has been found that symmetrical 1,3-diaroylureas can be prepared in good yields by allowing urea to react with aromatic esters and excess sodium hydride in refluxing 1,2-dimethoxyethane. Applications of this method to the synthesis of unsymmetrical 1,3-diaroylureas and substituted monoaroylureas are also described.

Canadian Journal of Chemistry, 47, 2097 (1969)

Can. J. Chem. Downloaded from www.nrcresearchpress.com by COLORADO COLLEGE - TUTT LIBRARY on 11/11/14 For personal use only.

In connection with a continuing study of basecatalyzed condensations involving nitrogencontaining carbonyl compounds (1, 2), we had occasion to investigate the reactions of urea and certain urea derivatives with aromatic esters, employing sodium hydride as the condensing agent. During the course of this investigation it became evident that these reactions provide a facile new method for the synthesis of 1,3diaroylureas. Unlike several previously reported methods (3-6), which are either inconvenient or of untested generality, the present procedure utilizes readily available starting materials and appears to be quite general in scope.

Results

Treatment of urea with slightly more than two molecular equivalents of the appropriate aromatic ester and excess sodium hydride in refluxing 1,2dimethoxyethane (DME) until hydrogen evolution was complete, produced symmetrical 1,3diaroylureas 1a-c, eq. [1]. Similarly, dibenzoylurea (1a) and unsymmetrical diaroylureas 2a-bwere obtained from the reaction of benzoylurea

$\rm NH_2CONH_2$	1. ArCOOCH ₃ ,	NaH
	2. Acid	
		ArCONHCONHCOAr
[1]		1a, Ar = C_6H_5
		b, Ar = C ₆ H ₄ Cl- p
		c. Ar = $C_6H_4OCH_3-p$

with methyl benzoate, methyl p-chlorobenzoate, and methyl anisate, respectively. In addition, this procedure was extended to the synthesis of monoaroylureas 3a-b, which were produced on treatment of methylurea and phenylurea with methyl

C₅H₅CONHCONHCOAr	RNHCONHCOC₅H₅
2a, Ar = C_6H_4Cl -p	3a, R = CH ₃
b, Ar = C ₆ H ₄ OCH ₃ - p	$b, R = C_6H_5$

benzoate and sodium hydride in refluxing DME. The results of these experiments are presented in Table I where it may be seen that yields were generally good to excellent. Incidentally, in an attempt to effect dibenzoylation of biuret by the above method, cleavage of one of the amide groups occurred and dibenzoylurea, instead of the expected dibenzoylation product of biuret, was isolated from the reaction.

Structural assignments for new diaroylureas 1b-c and 2a-b were based on analyses (Table I)

2097

¹Supported by the United States Public Health Service, Research Grant No. GM-14340 from the National Institute of General Medical Sciences.

CANADIAN JOURNAL OF CHEMISTRY. VOL. 47, 1969

TABLE I

Synthesis and properties of diaroylureas and substituted monoaroylureas

Starting material	Methyl ester	Product	Reaction period, h	Yield, %	Melting point, °C
Urea	Benzoate	1.3-Dibenzovlurea (1a)	4	98	212-2134,6
Urea	p-Chlorobenzoate	1.3-Di(<i>p</i> -chlorobenzovl)urea $(1b)^{c}$	2.5	80	241-243 ^d
Urea	Anisate	1.3-Dianisylurea $(1c)^{c}$	6.5	66	212.5-213.54
Benzovlurea	Benzoate	1.3-Dibenzovlurea $(1a)$	3	88	212-2134.6
Benzovlurea	p-Chlorobenzoate	1-Benzovl-3-(p-chlorobenzovl) urea $(2a)^{f}$	6	76	207-209ª
Benzovlurea	Anisate	1-Benzovl-3-anisylurea $(2b)^g$	4	37	202-204ª
Methylurea	Benzoate	1-Benzovl-3-methylurea $(3a)$	4	67	170-171**
Phenylurea	Benzoate	1-Benzoyl-3-phenylurea (3b)	1	90	209-210 ^a , ^j
*Recrystallized *Lit. (5) m.p. 20 *Anal. Calcd. ft *Recrystallized *Anal. Calcd. ft *Anal. Calcd. ft *Anal. Calcd. ft *Recrystallized *Dixon (7) repo *Lit. (5) m.p. 2	from absolute ethanol. $18-209^{\circ}$, or $C_{15}H_{10}N_2O_3Cl_2$: C, 53.4 from acetic acid. or $C_{17}H_{16}N_2O_3$: C, 62.19; or $C_{17}H_{16}N_2O_3$: C, 62.39; or $C_{16}H_{14}N_2O_4$: C, 59.5] or $C_{16}H_{14}N_2O_4$: C, 64.42; from 95% ethanol. rist m.p. 170–171°. 10°.	43; H, 2.99; N, 8.31; Cl, 21.03. Found: C, 53.23; H, 2 H, 4.91; N, 8.53. Found: C, 62.15; H, 4.86; N, 8.37 I; H, 3.66; N, 9.26; Cl, 11.71. Found: C, 59.51; H, 3.8 H, 4.73; N, 9.39. Found: C, 64.34; H, 4.81; N, 9.42.	2.96; N, 8.29; ; ;2; N, 9.48; C	Cl, 20.94.	· · ·

and spectral data. The i.r. spectra of these compounds, which were similar to that of dibenzoylurea, had strong NH absorption at 3360-3400 and two intense carbonyl bands at 1670 and 1750 cm^{-1} . The nuclear magnetic resonance (n.m.r.) spectra had absorption for two NH protons at 12.1-13.2 and resonance for the appropriate number of aromatic protons at 7.8-8.5 p.p.m.; the methoxy protons of 1c (6H) and 2b (3H) appeared as singlets at 4.0 and 4.3 p.p.m., respectively.

Experimental²

Synthesis of Symmetrical Diaroylureas 1a-c

These reactions were carried out in a 11 two-necked flask equipped with a heating mantle, a magnetic stirring bar, and a reflux condenser, connected at its upper end through a cold trap (dry ice - acetone) to a Precision Scientific wet-test meter filled with water. The other neck of the flask was connected, through rubber tubing, to a 150 ml round-bottomed flask. The reaction flask was charged with 250 ml of DME³ and 0.50 mole of sodium hydride,⁴ and a slurry of 0.05 mole of urea and 0.125 mole of the appropriate ester in 60 ml of DME was placed in the addition flask. The system was then flushed with dry nitrogen and closed to the atmosphere. The sodium hydride - DME slurry was brought to reflux, and when thermal equilibrium had been established (15-20 min) an initial reading was taken on the test meter. The slurry of urea and ester in DME was then added during 5-7 min. Readings were taken periodically on the gas meter until hydrogen evolution had ceased.⁵ Most of the solvent was then removed to give a pasty residue, which was cooled to 0° in an ice-water bath. Ether (150 ml) was added, and the resulting suspension was allowed to stir for 5-10 min. Cold water (100 ml) was added cautiously, and the solid which separated between the layers was collected by filtration and acidified with cold 6 N HCl. The resulting solid was collected, washed with 5% sodium bicarbonate solution, and recrystallized from the appropriate solvent (see Table I). Yields and analytical data for 1a-c are presented in Table I.

Synthesis of Unsymmetrical Diaroylureas 2a-b and Substituted Monoaroylureas 3a-b

These reactions were effected essentially as described above, employing 0.05 mole of the appropriate substituted urea, 0.08 mole of the appropriate aromatic ester, and 0.25 mole of sodium hydride. The reaction mixture was refluxed until hydrogen evolution ceased,⁶ and the reaction mixture was processed in the usual manner. Recrystallization solvents, yields, and analytical data for the products obtained from these reactions are presented in Table I.

²Melting points were taken on a Thomas-Hoover "Uni-Melt" apparatus in open capillary tubes, and are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Miss Q. H. Tan using an F & M model 185 C, H, and N analyzer. Infra-diated in the performance of the perfor red (i.r.) spectra were taken on a Beckman IR-5A infrared spectrophotometer using the potassium bromide pellet method. Nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to internal tetramethylsilane, were measured to the center of a singlet or multiplet. Dimethyl sulfoxide- d_6 was used as the n.m.r. solvent. Unless specified otherwise, chemicals were commercial reagent grade and were used without further purification. ³The DME was distilled from sodium ribbon immedi-

ately before use.

⁴This reagent was used as a 55% dispersion in mineral oil as obtained from Metal Hydrides, Inc., Beverly, Massachusetts.

⁵In all of these experiments four molecular equivalents of hydrogen were evolved.

⁶Three molecular equivalents of hydrogen were liberated in these experiments.

Attempted Dibenzoylation of Biuret

To a suspension of 0.50 mole of sodium hydride in 250 ml of refluxing DME was added a solution of 5.16 g (0.05 mole) of biuret and 17.02 g (0.125 mole) of methyl benzoate in 150 ml of DME. The reaction mixture was refluxed for 19.5 h and then processed in the usual manner to afford, after one recrystallization from absolute ethanol, 5.10 g (38%) of 1,3-dibenzoylurea (1a), m.p. 215-217°; mixture m.p. 215-217°. The i.r. spectrum of this material was identical with that of a sample of 1a prepared from the dibenzoylation of urea.

NOTES

- 1. J. F. WOLFE and G. B. TRIMITSIS. J. Org. Chem. 33, 894 (1968).
- J. F. WOLFE, G. B. TRIMITSIS, and C. R. HAUSER. Can. J. Chem. 46, 2561 (1968). 2.
- E. SCHMIDT. J. prakt. Chem. [2], 5, 58 (1872).
 A. F. HOLLEMAN. Chem. Ber. 23, 3000 (1890).
 O. C. BILLETER. Chem. Ber. 36, 3218 (1903).

- R. A. JACOBSEN. U.S. Patent 2,090,593 (1937); Chem. Abst. 31, 7068 (1937). 6. R.
- 7. A. E. DIXON. J. Chem. Soc. 75, 383 (1899).

Selective reduction of esters with sodium trimethoxyborohydride

R. A. Bell and M. B. Gravestock McMaster University, Hamilton, Ontario Received December 27, 1968

The rate of reduction of representative methyl esters with sodium trimethoxyborohydride decreases in the order primary > secondary > tertiary. Sodium trimethoxyborohydride reduces with 100%selectivity the secondary ester group in the alicyclic diester-acid 2c.

Canadian Journal of Chemistry, 47, 2099 (1969)

Can. J. Chem. Downloaded from www.nrcresearchpress.com by COLORADO COLLEGE - TUTT LIBRARY on 11/11/14 For personal use only.

Since its first preparation and brief examination of its properties in 1953 by Brown and Mead (1), sodium trimethoxyborohydride appears to have received little attention by organic chemists (2). We now report the 100% selective reduction of the alicyclic diester-acid 2c with sodium trimethoxyborohydride in refluxing dimethoxyethane. In order to gauge the synthetic utility of this reagent in selective ester reductions, we have measured the rates of reduction of the primary, secondary, and tertiary methyl esters, methyl 3-phenylpropionate, methyl cyclohexylcarboxylate, and methyl abietate 4.

The diester-acid 2c was prepared from the known compound (3) methyl 12-oxopodocarp-13-en-16-oate 1. Ozonolysis of 1 in ethyl acetate at 0°, followed by treatment with hydrogen peroxide in acetic acid yielded a dicarboxylic acid 2a, which on methylation with diazomethane afforded the triester 2b. Selective hydrolysis with one mole-equivalent of sodium hydroxide in methanol (4) yielded the diester-acid 2c in 75% overall yield from 1.

The selective reduction of the secondary ester function in 2c was accomplished by treatment with a three mole-equivalent excess of sodium trimethoxyborohydride in refluxing dimethoxyethane. The ester – acid – alcohol 3 was obtained in greater than 95% yield, either as the free



alcohol or in the form of its δ -lactone. Careful examination of the crude reaction product by proton magnetic resonance (p.m.r.) spectroscopy showed that the C-15 carbomethoxy group at 3.64 p.p.m. had suffered no observable reduction. The

2099