HETEROCYCLES, Vol 22, No. 3, 1984

SYNTHESIS OF FURO[3,4-*d*]PYRIMIDINE DERIVATIVES USING ETHYL 4-BROMOACETOACETATE

Takuo Chiba,* Hirotoshi Sato, and Tetsuzo Kato
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

Abstract —— Reaction of ethyl 4-bromoacetoacetate (1)' with benzaldehyde (2a) and urea in the presence of hydrochloric acid gave 6-bromomethyl-5-ethoxycarbonyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone (3a). Similarly, reaction of 1 and urea with *p*-anisaldehyde (2b), *p*-hydroxybenzaldehyde (2c), and furfural (2d) afforded the corresponding 6-bromomethyl-3,4-dihydro-2(1*H*)-pyrimidinones 3b-3d.
Thermolysis of compounds 3a-3d gave rise to the corresponding 4,7-dihydrofuro[3,4-*d*]pyrimidine-2,5(1*H*,3*H*)-diones 4a-4d.

The Feist-Bénary[1] reaction of ethyl 4-bromoacetoacetate (1) with chloroacetaldehyde was reported to give 2-bromomethylfuran derivative.[2] On the other hand, we have reported the reaction of 1 with diketene to give ethyl ω-bromoorsellinate.[3] In these reactions, the ketocarbonyl and active methylene groups of 1 take part in the ring formation. Since there are few references concerning such a ring formation using 1, we have investigated the Biginelli[4] reaction of 1 in a continuation of our study on the synthesis of heterocyclic compounds using haloacetoacetic acid derivatives.[5-7]

When a solution of ethyl 4-bromoacetoacetate (1), benzaldehyde (2a), and urea in ethanol in the presence of hydrochloric acid was warmed at 40°C for 24 h, 6-bromomethyl-5-ethoxycarbonyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone (3a)[8] was obtained in 62% yield. The structure assignment was established by spectroscopic data. Infrared (ir) spectrum of 3a indicated the presence of α,β-unsaturated ester carbonyl and ureido carbonyl absorption at 1690 and 1640 cm^{-1}, respectively. Nuclear magnetic resonance (nmr) spectrum of 3a showed the signals due to methylene protons, the C_4-methine proton, and two ureido protons.

Similarly, the Biginelli reaction using 1 and aromatic aldehydes such as *p*-anisaldehyde (2b), *p*-hydroxybenzaldehyde (2c), and furfural (2d) under the same condition afforded the corresponding 6-bromomethyl-3,4-dihydro-2(1*H*)-pyrimidinones 3b-3d in 43-57% yields.

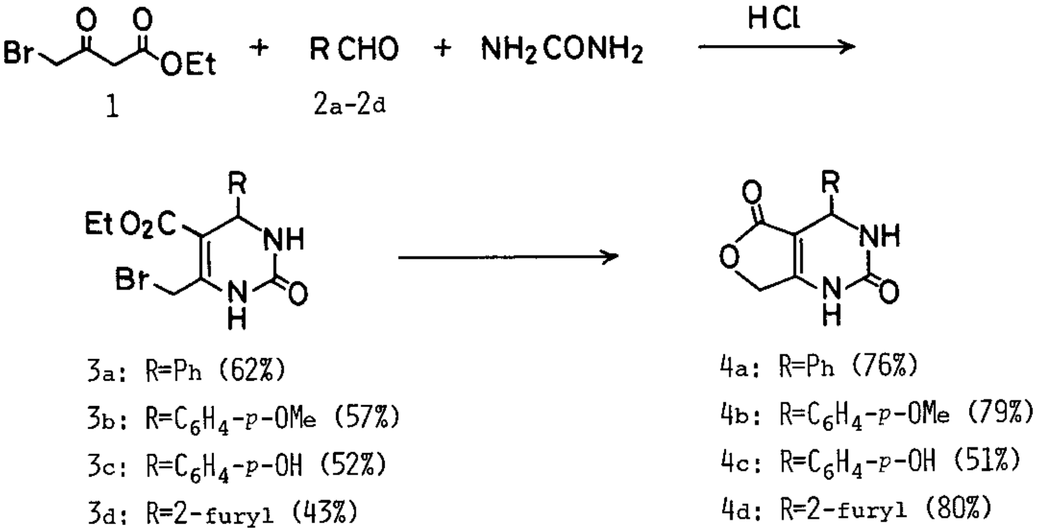

Chart 1

Heating of compound 3a at 210-230°C gave 4-phenyl-4,7-dihydrofuro[3,4-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (4a)[9] in 76% yield.

Similarly, thermolysis of 3b-3d gave rise to the corresponding 4,7-dihydrofuro-[3,4-*d*]pyrimidine-2,5(1*H*,3*H*)-diones 4b-4d in 51-80% yields. These results are also consistent with the indicated structure of 3a-3d. The melting points and ir spectra for 3a-3d and 4a-4d are listed in Table I.

Table I. Melting Points and ir Spectra for 3a-3d and 4a-4d

No.	mp (°C) (dec.)	$\nu_{max.}$ (Nujol) cm^{-1}
3a	172-173	3370, 3220, 1690, 1640
3b	162-163	3375, 3200, 1690, 1640
3c	151-152	3250, 1680, 1650
3d	164-165	3400, 3240, 1690, 1640
4a	262-264	3225, 3180, 1730, 1690, 1670
4b	272-273	3350, 3200, 1730, 1690, 1670
4c	279-281	3300, 1735, 1690, 1670
4d	252-254	3325, 3200, 1730, 1695, 1665

ACKNOWLEDGEMENT

The authors are indebted to the Central Analysis Room of this Institute for elemental analyses and spectral measurements.

REFERENCES AND NOTES

1. a) F. Feist, *Ber.*, 1902, 35, 1537, 1545.
   b) E. Bénary, *Ber.*, 1911, 44, 489, 493.
2. a) E. Bisagni and C. Rivalle, *Bull. Soc. Chim. Fr.*, 1974, 519.
   b) R. Y. Mauvernay, Ger. Patent 2 444 453 (1975) [*Chem. Abstr.*, 1975, 83, 79062s].
3. T. Kato, M. Sato, and H. Kimura, *J. Chem. Soc., Perkin Trans. 1*, 1979, 529.

4. P. Biginelli, *Ber.*, 1891, 24, 1317, 2962.
5. T. Chiba, H. Sato, and T. Kato, *Chem. Pharm. Bull.*, 1982, 30, 3548.
6. *Idem, ibid.*, 1983, 31, 2480.
7. T. Chiba, H. Sato, T. Kayaba, and T. Kato, *Heterocycles*, submitted.
8. 6-Bromomethyl-5-ethoxycarbonyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone (3a) —— A mixture of ethyl 4-bromoacetoacetate (1) (2.1 g, 0.01 mol), benzaldehyde (2a) (1.1 g, 0.01 mol), urea (1.2 g, 0.02 mol), and 10% hydrochloric acid (5 ml) in ethanol (10 ml) was stirred at 40°C for 24 h. The reaction mixture was cooled on an ice bath. Separated crystals were collected and recrystallized from ethyl acetate to give the product 3a as colorless prisms. Yield, 2.1 g (62%). δ (CF_3CO_2H) 1.20 (3H, t, *J* 7 Hz, $CH_2C\underline{H}_3$), 4.21 (2H, q, *J* 7 Hz, $OC\underline{H}_2CH_3$), 4.82 (2H, s, CH_2Br), 5.64 (1H, br s, 4-H), 7.05-7.50 (6H, br, NH and Ph), and 8.40-8.77 (1H, br, NH); *m/e* 340 (M^++2), 338 (M^+), and 258 (M^+-HBr).
9. 4-Phenyl-4,7-dihydrofuro[3,4-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (4a) —— Compound 3a (0.68 g, 2 mmol) was heated on a silicone oil bath at 210-230°C. The residue was purified by recrystallization from methanol to afford the product 4a as colorless needles. Yield, 0.35 g (76%). δ (CF_3CO_2H) 5.09 (2H, s, CH_2O), 5.60 (1H, s, 7-H), 7.01-7.30 (1H, br, NH), 7.37 (5H, s, Ph), and 8.87-9.17 (1H, br, NH).

Received, 24th November, 1983