

Chaitanya G. Dave* and Manish C. Shukla [1]

Organic Synthesis Laboratory, M. G. Science Institute, Navrangpura, Ahmedabad 380 009, India

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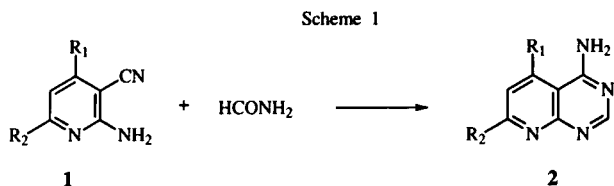
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Diethyl ethoxymethylenemalonate was used for the novel synthesis of the triheterocyclic 3-carbethoxy-9,11-disubstituted-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines from 4-aminopyrido[2,3-*d*]pyrimidines *via* thermal cyclization of the intermediate ethyl 2-carbethoxy-3-[5,7-disubstituted-4-amino-pyrido[2,3-*d*]pyrimidin-4-yl]acrylates. The alkaline hydrolysis of 3-carbethoxy-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines was performed to give corresponding acid derivatives.

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Diethyl ethoxymethylenemalonate is widely used in the push-pull alkane [2], 1,4-addition-elimination [3], 1,4-addition [4], 3+2 cycloaddition [5], protecting group of amino acids [6], and Diels-Alder reactions [7]. It is also useful in the synthesis of quinoline derivatives by the Gould-Jacob reaction [8]. In a similar fashion various heterocycles such as 1,8-naphthyridines, 2*H*-pyrido[1,2-*a*]pyrimidin-4-ones, pyrazolinones, pyrones, xanthyrones, guanidine derivatives, 1,2,4-triazoles, 3-oxo-1,2,6-thiadiazines, 8-oxoimidazo[1,2-*a*]pyrimidines, 3*H*-pyrrolo[1,2-*a*]indol-3-one derivatives and 1*H*-1,4-benzodiazapines can be obtained [9]. However, no attention has been given to the synthesis of angular triheterocyclic pyridopyrimidopyrimidines using diethyl ethoxymethylenemalonate as a synthon. Therefore, in continuation of our interest in fused bi- and triheterocycles [10-12], we report herein, the first ever synthesis of pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines using diethyl ethoxymethylenemalonate.

4-Amino-5,7-disubstitutedpyrido[2,3-*d*]pyrimidines **2** required for the synthesis of pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines **4**, were synthesized by reacting 2-amino-3-cyano-4,6-disubstitutedpyridines **1** and formamide [13,14] (Scheme 1).

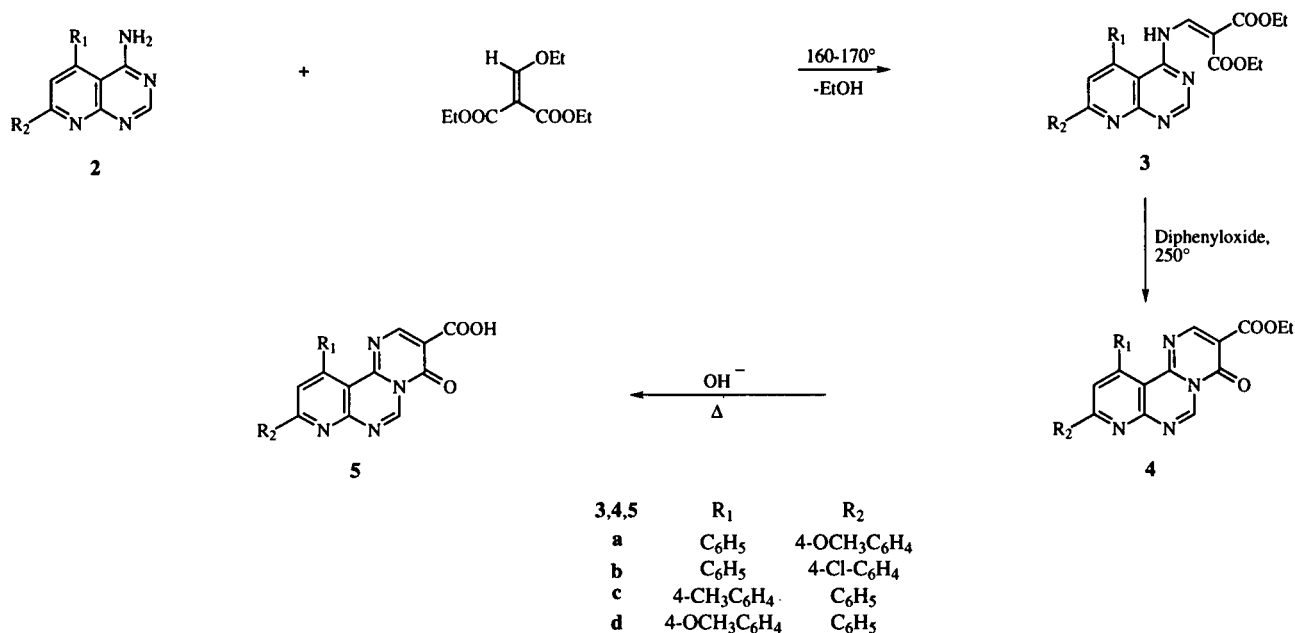


4-Aminopyrido[2,3-*d*]pyrimidines **2** were heated with diethyl ethoxymethylenemalonate at 120-130° for 2-4 hours to give the intermediate uncyclized ethyl 2-carbethoxy-3-[5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylates **3** in 50-70% yields, which were cyclized thermally in boiling diphenyl oxide to obtain 3-carbethoxy-9,11-disubstituted-4-oxo-4*H*-pyrido[3,2-*e*]pyrim-

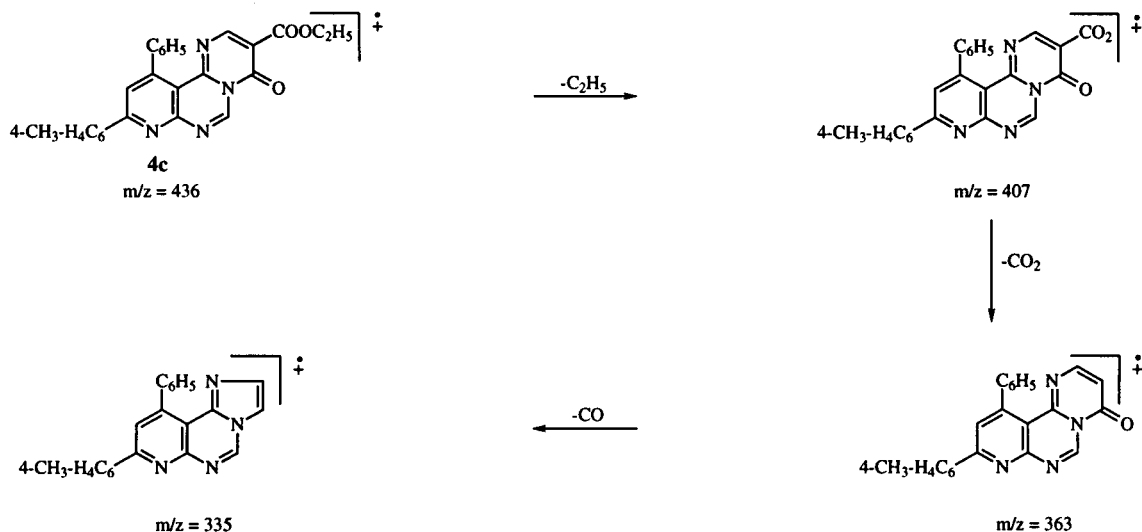
ido[1,2-*c*]pyrimidines **4** in 55-75% yields. Compounds **4** were hydrolyzed using alcoholic potassium hydroxide (20% w/v) at reflux temperature to obtain the corresponding acid derivatives, 9,11-disubstituted-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylic acids **5** (Scheme 2).

The uv spectra of ethyl 2-carbethoxy-3-[5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylates **3** exhibited two to three bands in the region 295-327 nm. The ir spectra of the compounds **3** displayed -NH stretching vibration around 3300 cm⁻¹. The two characteristic absorption bands were found in the region 1712-1669 cm⁻¹ due to the presence of two carbonyl groups. The ¹H-nmr spectrum of ethyl 2-carbethoxy-3-[5-(4-methylphenyl)-7-phenyl-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylate (**3c**) showed two triplets at δ 1.12-1.59 and two quartets at δ 4.29-4.44 which were assigned to the presence of two ethyl (-CH₂CH₃) groups. Moreover, a singlet at δ 2.45 and a multiplet at δ 7.0-8.0 were found integrating for 3H (CH₃) and Ar-H (aromatic protons) respectively. The mass spectrum of compound **3c** (m/z = 481) showed a fragment at m/z 436. This ion was identified as [M⁺-COOC₂H₅] confirming the non-cyclized structure **3c**. The uv spectra of 3-carbethoxy-9,11-disubstituted-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines **4** showed two to three different bands in the region 245-336 nm. In their ir spectra, two characteristic bands appeared between 1740-1690 cm⁻¹ for carbonyl stretching. These C=O stretching vibrations were shifted 20-40 cm⁻¹ to a higher wave number as compared to non-cyclized acrylates **3**. The cyclic ketone is responsible for this characteristic behavior. Absence of an -NH stretching vibration in the region 3300 cm⁻¹ supported the cyclic structure **4**. The ¹H-nmr spectrum of compound **4c** exhibited a triplet at δ 1.12-1.70 and a quartet at δ 4.29-4.29 which was suggestive of the presence of one -CH₂CH₃ group. The nmr spectrum also showed a singlet at δ 2.44 for methyl protons. The mass spectrum of compound **4c** displayed abun-

Scheme 2



Scheme 3



dant M^+ ions. The fragment ion $[\text{M}^+ - \text{COOC}_2\text{H}_5]$ was obtained at m/z 363. The fragmentation pattern is depicted in Scheme 3.

The uv spectral data of 9,11-disubstituted-4-oxo-4H-pyrido[3,2-e]pyrimido[1,2-c]pyrimidine-3-carboxylic acids 5 displayed two to three different bands in the region 240-525 nm. The ir spectra of compounds 5 showed a characteristic broad band between 3500-3200 cm^{-1} which suggested the presence of the carboxylic -OH

group. Two strong absorption appeared at 1728-1644 cm^{-1} which were due to the presence of $\text{C}=\text{O}$ groups. The ^1H -nmr and mass spectra of compounds 5 could not be obtained because of poor solubility.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. The uv spectra were recorded on Beckman DU-64 spectrophotometer using spectroscopic grade methylene

chloride as the solvent. The ir spectra were run on Buck-Scientific spectrophotometer Model 500. The ir spectra were acquired for the compounds synthesized by coating the compound on potassium bromide plates. The ^1H -nmr spectra were recorded on a Varian Model 400 spectrometer using tetramethylsilane as the internal reference (chemical shifts in δ ppm). Mass spectra were run on Jeol JMS-D Model 300. The purity of the compounds synthesized was checked by tlc using silica gel-G plates (1 mm thickness) and iodine vapor was used to reveal the spot.

General Procedure for the Preparation of Ethyl 2-Carboxy-3-[5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylates 3a-e.

A mixture of 4-amino-5,7-disubstitutedpyrido[2,3-*d*]pyrimidines **2**, (0.01 mole), diethyl ethoxymethylenemalonate (0.001 mole) and diphenyl oxide (6.0 ml) was heated at 170-180° for 3 hours. During the reaction, the ethanol produced was distilled continuously. The reaction mixture was cooled to room temperature to obtain a solid which was filtered and washed with cold ethanol. The dried crude product was crystallized from *N,N*-dimethylformamide.

Ethyl 2-Carboxy-3-[5-phenyl-7-(4-methoxyphenyl)-4-amino-pyrido[2,3-*d*]pyrimidin-4-yl] acrylate (3a).

This compound had the following physical properties: yield 66%, mp 166-167°; uv: λ max (log *e*) 337 (4.123), 295 (4.186); ir (potassium bromide): 3300 (NH), 1706, 1676 (C=O); ^1H -nmr: δ 1.10-1.60 (3H, t, $-\text{CH}_2\text{CH}_3$), 3.90 (3H, s, $-\text{OCH}_3$), 4.30-4.70 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.46-7.90 (11H, m, Ar-H); ms: (70 ev) *m/z* 498 (100% M^+).

Anal. Calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$: C, 67.45; H, 5.25; N, 11.24. Found: C, 67.11; H, 5.02; N, 11.51.

Ethyl 2-Carboxy-3-[5-phenyl-7-(4-chlorophenyl)-4-amino-pyrido[2,3-*d*]pyrimidin-4-yl]acrylate (3b).

This compound had the following physical properties: yield 50%, mp 193-195°; uv: λ max (log *e*) 325 (4.165), 295 (4.172); ir (potassium bromide): 3300 (NH), 1706, 1676 (C=O); ^1H -nmr: δ 1.10-1.61 (3H, t, $-\text{CH}_2\text{CH}_3$), 4.3-4.7 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.46-7.90 (11H, m, Ar-H); ms: (70 ev) *m/z* 504.5 (58% $\text{M} + 2$).

Anal. Calcd. for $\text{C}_{27}\text{H}_{23}\text{ClN}_4\text{O}_4$: C, 64.55; H, 4.61; N, 11.14. Found: C, 64.73; H, 4.98; N, 11.39.

Ethyl 2-Carboxy-3-[5-(4-methylphenyl)-7-phenyl-4-amino-pyrido[2,3-*d*]pyrimidin-4-yl]acrylate (3c).

This compound had the following physical properties: yield 68%, mp 159-160°; uv: λ max (log *e*) 317 (4.175), 295 (4.186); ir (potassium bromide): 3300 (NH), 1706, 1676 (C=O); ^1H -nmr: δ 1.12-1.60 (3H, t, $-\text{CH}_2\text{CH}_3$), 2.46 (3H, s, $-\text{CH}_3$), 4.30-4.44 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.52-7.83 (11H, m, Ar-H); ms: (70 ev) *m/z* 482 (100% M^+).

Anal. Calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_4$: C, 69.69; H, 5.43; N, 10.99. Found: C, 70.01; H, 5.77; N, 11.21.

Ethyl 2-Carboxy-3-[5-(4-methoxyphenyl)-7-phenyl-4-amino-pyrido[2,3-*d*]pyrimidin-4-yl]acrylate (3d).

This compound had the following physical properties: yield 58%, mp 104-105°; uv: λ max (log *e*) 320 (4.009), 295 (4.178); ir (potassium bromide): 3300 (NH), 1706, 1676 (C=O); ^1H -nmr: 1.13-1.60 (3H, t, $-\text{CH}_2\text{CH}_3$), 3.86 (3H, s, $-\text{CH}_3$), 4.40-4.85 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.50-7.88 (11H, m, Ar-H).

Anal. Calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$: C, 67.45; H, 5.25; N, 11.24. Found: C, 67.70; H, 5.02; N, 11.49.

General Procedure for the Preparation of 3-Carboxy-9,11-disubstituted-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines 4a-e.

Ethyl 2-carboxy-3-[5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylates **3** (2.0 g.) was carefully poured into boiling diphenyl oxide (6.0 ml) and heated 250° for 45 minutes. The reaction mixture was allowed to cool to room temperature and diluted with *n*-hexane (30 ml). The solid was filtered, washed with *n*-hexane followed by cold ethanol and dried. The dried crude product was crystallized from *N,N*-dimethylformamide.

3-Carboxy-9-(4-methoxyphenyl)-11-phenyl-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine 4a.

This compound had the following physical properties: yield 63%, mp 261-263°; uv: λ max (log *e*) 325 (4.137), 249 (4.156); ir (potassium bromide): 1748, 1700 (C=O); ^1H -nmr: δ 1.25-1.70 (3H, s, $-\text{CH}_2\text{CH}_3$), 4.07 (3H, s, $-\text{CH}_3$), 4.3-4.7 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.49-8.27 (12H, m, Ar-H); ms: (70 ev) *m/z* 452 (100% M^+).

Anal. Calcd. for $\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_4$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.87; H, 4.79; N, 12.29.

3-Carboxy-9-(4-chlorophenyl)-11-phenyl-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine (4b).

This compound had the following physical properties: yield 74%, mp 265-267°; uv: λ max (log *e*) 357 (3.899), 249 (4.123); ir (potassium bromide): 1724, 1692 (C=O); ^1H -nmr: δ 1.20-1.66 (3H, t, $-\text{CH}_2\text{CH}_3$), 4.32-4.71 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.55-8.38 (12H, m, Ar-H).

Anal. Calcd. for $\text{C}_{25}\text{H}_{17}\text{ClN}_4\text{O}_3$: C, 65.72; H, 3.75; N, 12.26. Found: C, 66.03; H, 3.51; N, 12.48.

3-Carboxy-9-(4-methylphenyl)-11-phenyl-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine (4c).

This compound had the following physical properties: yield, 61%, mp 218-220°; uv: λ max (log *e*) 353 (4.078), 249 (4.153); ir (potassium bromide): 1736, 1690 (C=O); ^1H -nmr: 1.2-1.7 (3H, t, $-\text{CH}_2\text{CH}_3$), 2.47 (3H, s, $-\text{CH}_3$), 4.29-4.44 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.53-8.30 (12H, m, Ar-H); ms: *m/z* 436 (100% M^+).

Anal. Calcd. for $\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_3$: C, 71.55; H, 4.62; N, 12.84. Found: C, 71.23; H, 4.44; N, 12.60.

3-Carboxy-9-(4-methoxyphenyl)-11-phenyl-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine (4d).

This compound had the following physical properties: yield 57%, mp 225-227°; uv: λ max (log *e*): 353 (4.001), 249 (4.123); ir (potassium bromide): 1740, 1698 (C=O); ^1H -nmr: δ 1.13-1.70 (3H, s, $-\text{CH}_2\text{CH}_3$), 4.1 (3H, s, $-\text{OCH}_3$), 4.35-4.75 (2H, q, $-\text{CH}_2\text{CH}_3$), 7.52-8.45 (12H, m, Ar-H); ms: *m/z* 452 (100% M^+).

Anal. Calcd. for $\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.38; H, 4.57; N, 12.02.

General Procedure for the Preparation of 9,11-Disubstituted-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylic Acid (5).

3-Carboxy-9,11-disubstituted-4-oxo-4H-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines **4** (1.0 g) were heated under reflux in alcoholic potassium hydroxide solution (10 ml, 20% w/v) for

two hours. The cooled reaction mixture was poured onto crushed ice and neutralized with dilute hydrochloric acid to pH 4. The solid was filtered, washed with water, dried and crystallized from ethanol.

9-(4-Methoxyphenyl)-11-phenyl-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylic Acid (**5a**).

This compound had the following physical properties: yield 59%, mp 235-237°; uv: λ max (log ϵ): 415 (3.929), 241 (4.125); ir (potassium bromide): 3400-3260 (OH), 1724, 1648 (C=O); ms: m/z 426 (100% M^+).

Anal. Calcd. for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found: C, 67.69; H, 4.53; N, 13.41.

9-(4-Methylphenyl)-11-phenyl-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylic Acid (**5b**).

This compound had the following physical properties: yield 83%, mp 243-245°; uv: λ max (log ϵ): 415 (4.039), 249 (3.977); ir (potassium bromide): 3400-3270 (OH), 1728, 1644 (C=O).

Anal. Calcd. for $C_{24}H_{18}N_4O_3$: C, 70.23; H, 4.42; N, 13.65. Found: C, 70.34; H, 4.60; N, 13.81.

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REFERENCES AND NOTES

- [1] Present address: Dishman Pharm. and Chem. pvt. Ltd; Ahmedabad 380 009, India.
- [2] J. Sandstroem, *Top. Stereochem.*, **14**, 83 (1983).
- [3] M. Ihara, K. Noguchi, T. Ohsawa, K. Fukumoto and T. Kametani, *J. Org. Chem.*, **48**, 3150 (1983).
- [4] S. Hibino, E. Sugino, T. Kuwada, N. Ogura, K. Soto and T. Choshi, *J. Org. Chem.*, **57**, 5917 (1992).
- [5] D. L. Boger and C. E. Brotherton, *J. Am. Chem. Soc.*, **108**, 6695 (1986).
- [6] M. Aliaz, J. Giron, F. J. Hidalgo, M. P. de la Maza, F. Millan, R. Zamora and E. Vioque, *Synthesis*, 544 (1989).
- [7] N. Katagiri, H. Akatsuka, T. Haneda, C. Kaneko and A. Sera, *J. Org. Chem.*, **53**, 5464 (1988).
- [8] R. G. Gould Jr. and W. A. Jacobs, *J. Amer. Chem. Soc.*, **61**, 2890 (1939).
- [9] Encyclopedia of Reagents for Organic Synthesis, Vol 3, L. A. Paquette, ed, John Wiley & Sons, 1995, p 1816.
- [10] C. G. Dave, P. R. Shah and A. B. Shah, *Indian J. Chem.*, **31B**, 492 (1992).
- [11] C. G. Dave, A. B. Shah and H. C. Shah, *J. Heterocyclic Chem.*, **34**, 937 (1997).
- [12] C. G. Dave and S. P. Upadhyaya, *Indian J. Heterocyclic Chem.*, **4**, 71 (1994).
- [13] T. A. Williamson, *Heterocyclic Compounds*, Vol 5, R. C. Elderfield, ed, John Wiley & Sons, New York, 1957, p 324.
- [14] W. J. Irwin and D. G. Wibberley, *Adv. Heterocyclic Chem.*, **10**, 149 (1969).