Diethyl Ethoxymethylenemalonate in Triheterocycles: A New Synthesis of Pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines

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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-aminopyrido[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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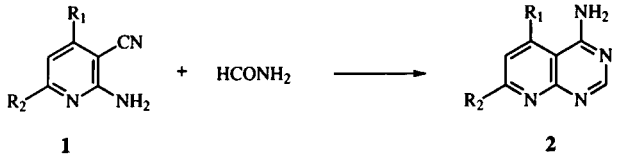
Diethyl ethoxymethylenemalonate is widely used in the push-pull alkane [2], 1,4-addition-elimination [3], 1,4-addition [4], 3+2 cycloaddition [5], protecting group of amino acids [6], and Diels-Alder reactions [7]. It is also useful in the synthesis of quinoline derivatives by the Gould-Jackob reaction [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).

Scheme 1

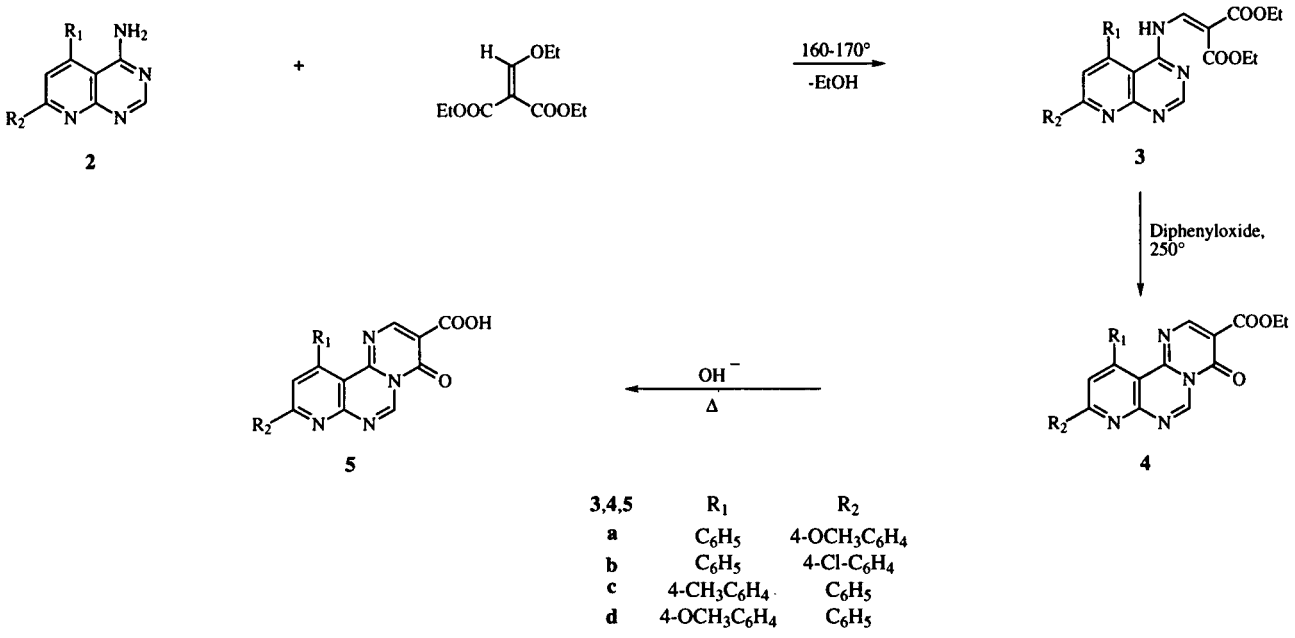


1 **2**

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*]pyrimido[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).

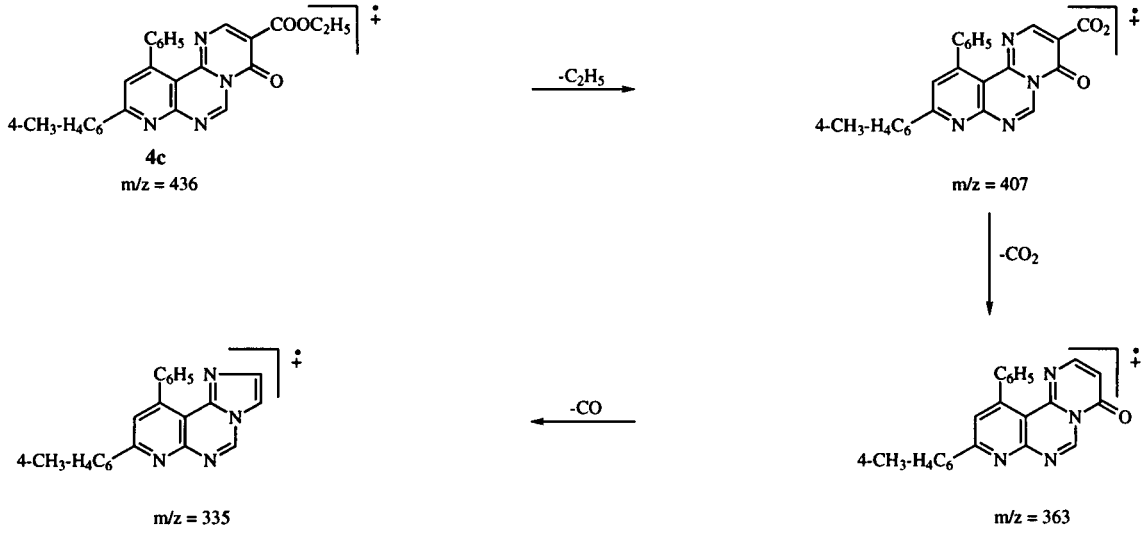
The uv spectra of ethyl 2-carbethoxy-3-[5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidin-4-yl]acrylates **3** exhibited two to three bands in the region 295-327 nm. The ir spectra of the compounds **3** displayed -NH stretching vibration around 3300 cm^{-1}. The two characteristic absorption bands were found in the region 1712-1669 cm^{-1} due to the presence of two carbonyl groups. The ^{1}H-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 ($-CH_2CH_3$) groups. Moreover, a singlet at δ 2.45 and a multiplet at δ 7.0-8.0 were found integrating for 3H (CH_3) 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^+-$COOC_2H_5$] 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 ^{1}H-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 $-CH_2CH_3$ 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



3,4,5	R_1	R_2
a	C_6H_5	4-$OCH_3C_6H_4$
b	C_6H_5	4-Cl-C_6H_4
c	4-$CH_3C_6H_4$	C_6H_5
d	4-$OCH_3C_6H_4$	C_6H_5

Scheme 3



4c
m/z = 436

m/z = 407

m/z = 363

m/z = 335

dant M^+ ions. The fragment ion [M^+-$COOC_2H_5$] was obtained at m/z 363. The fragmentation pattern is depicted in Scheme 3.

The uv spectral data of 9,11-disubstituted-4-oxo-4*H*-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 C=O groups. The ^{1}H-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 ^{1}H-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-Carbethoxy-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-Carbethoxy-3-[5-phenyl-7-(4-methoxyphenyl)-4-aminopyrido[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); ^{1}H-nmr: δ 1.10-1.60 (3H, t, -CH_2CH_3), 3.90 (3H, s, -OCH_3), 4.30-4.70 (2H, q, -CH_2CH_3), 7.46-7.90 (11H, m, Ar-H); ms: (70 ev) m/z 498 (100% M$^+$).

Anal. Calcd. for $C_{28}H_{26}N_4O_5$: C, 67.45; H, 5.25; N, 11.24. Found: C, 67.11; H, 5.02; N, 11.51.

Ethyl 2-Carbethoxy-3-[5-phenyl-7-(4-chlorophenyl)-4-aminopyrido[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); ^{1}H-nmr: δ 1.10-1.61 (3H, t, -CH_2CH_3, 4.3-4.7 (2H, q, -CH_2CH_3), 7.46-7.90 (11H, m, Ar-H); ms: (70 ev) m/z 504.5 (58% M + 2).

Anal. Calcd. for $C_{27}H_{23}ClN_4O_4$: C, 64.55; H, 4.61; N, 11.14. Found: C, 64.73; H, 4.98; N, 11.39.

Ethyl 2-Carbethoxy-3-[5-(4-methylphenyl)-7-phenyl-4-aminopyrido[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); ^{1}H-nmr: δ 1.12-1.60 (3H, t, -CH_2CH_3, 2.46 (3H, s, -CH_3), 4.30-4.44 (2H, q, -CH_2CH_3), 7.52-7.83 (11H, m, Ar-H); ms: (70 ev) m/z 482 (100% M$^+$).

Anal. Calcd. for $C_{28}H_{26}N_4O_4$: C, 69.69; H, 5.43; N, 10.99. Found: C, 70.01; H, 5.77; N, 11.21.

Ethyl 2-Carbethoxy-3-[5-(4-methoxyphenyl)-7-phenyl-4-aminopyrido[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); ^{1}H-nmr: 1.13-1.60 (3H, t, -CH_2CH_3), 3.86 (3H, s, -CH_3), 4.40-4.85 (2H, q, -CH_2CH_3), 7.50-7.88 (11H, m, Ar-H).

Anal. Calcd. for $C_{28}H_{26}N_4O_5$: 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-Carbethoxy-9,11-disubstituted-4-oxo-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidines **4a-e**.

Ethyl 2-carbethoxy-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-Carbethoxy-9-(4-methoxyphenyl)-11-phenyl-4-oxo-4*H*-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); ^{1}H-nmr: δ 1.25-1.70 (3H, s, -CH_2CH_3), 4.07 (3H, s, -CH_3), 4.3-4.7 (2H, q, -CH_2CH_3), 7.49-8.27 (12H, m, Ar-H); ms: (70 ev) m/z 452 (100% M$^+$).

Anal. Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.87; H, 4.79; N, 12.29.

3-Carbethoxy-9-(4-chlorophenyl)-11-phenyl-4-oxo-4*H*-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); ^{1}H-nmr: δ 1.20-1.66 (3H, t, -CH_2CH_3), 4.32-4.71 (2H, q, -CH_2CH_3), 7.55-8.38 (12H, m, Ar-H).

Anal. Calcd. for $C_{25}H_{17}ClN_4O_3$: C, 65.72; H, 3.75, N, 12.26. Found: C, 66.03; H, 3.51; N, 12.48.

3-Carbethoxy-9-(4-methylphenyl)-11-phenyl-4-oxo-4*H*-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); ^{1}H-nmr: 1.2-1.7 (3H, t, CH_2CH_3), 2.47 (3H, s, -CH_3), 4.29-4.44 (2H, q, -CH_2CH_3), 7.53-8.30 (12H, m, Ar-H); ms: m/z 436 (100% M$^+$).

Anal. Calcd. for $C_{26}H_{20}N_4O_3$: C, 71.55; H, 4.62, N, 12.84. Found: C, 71.23; H, 4.44; N, 12.60.

3-Carbethoxy-9-(4-methoxyphenyl)-11-phenyl-4-oxo-4*H*-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); ^{1}H-nmr: δ 1.13-1.70 (3H, s, -CH_2CH_3, 4.1 (3H, s, -OCH_3), 4.35-4.75 (2H, q, -CH_2CH_3), 7.52-8.45 (12H, m, Ar-H); ms: m/z 452 (100% M$^+$).

Anal. Calcd. for $C_{26}H_{20}N_4O_4$: 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-4*H*-pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylic Acid (**5**).

3-Carbethoxy-9,11-disubstituted-4-oxo-4*H*-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 *p*H 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 e) 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 e): 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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