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A Novel One-Pot Procedure for Preparation of Some New Condensed Pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones

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ABSTRACT: *A novel one-pot procedure for preparation of some new condensed pyrido[2,3-d]pyrimidine(1H,3H)-2,4-diones based on condensation of ninhydrin, alkyl cyanoacetate, and 6-aminouracil derivatives has been reported. The reactions were carried out in refluxed ethanol and were completed in less than 2 h.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:16–18, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20242

INTRODUCTION

Pyrido[2,3-*d*]pyrimidines are annelated uracils which have received considerable attention over the past years due to their wide range of biological activity [1]. Among these, pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones are of great interest because of their antitumor, antifolate, growth regulator etc. activities [2]. In the midst of methods for the synthesis of pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones, the condensation of 6-aminouracil derivatives with the suitable electrophiles is a straightforward and often used approach [3]. However, many of these reactions suffer from low yields, use of expensive or not readily available starting materials, and exhibiting limited substrate tolerance. In view of these facts, development of alternative one-pot procedures is crucial.

In our continued interest [4] in the development of highly expedient methods for the synthesis of various heterocyclic systems and as part of our ongoing programs on one-pot multi-component reactions (MCR)s [5], we report in this paper a novel one-pot route for the synthesis of some new condensed pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones (Scheme 1).

RESULTS AND DISCUSSION

The experimental procedure is simple: equimolar amount of ninhydrin **1**, 6-amino-uracil **2**, and alkyl cyanoacetate **3** in ethanol was refluxed for 2 h. The reactions proceeded smoothly at refluxed ethanol, and the products were obtained in good yields **4** (Scheme 1).

The structures of compounds **4a–d** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectrum of **4b** displayed the molecular ion peak (M^+) at $m/z = 351$, which is consistent with its proposed structure.

The ^{1}H NMR spectrum exhibited three singlets at δ 3.48, 3.87, and 4.14 which readily recognized

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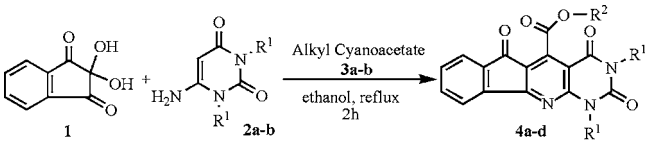


4	R^1	R^2	% Yield
a	Me	Et	80
b	Me	Me	75
c	H	Et	83
d	H	Me	70

SCHEME 1

as arising from two N-methyl and O-methyl protons of carboxylic ester, respectively. The characteristic multiplets for the aromatic protons are located at $\delta = 7.46$–7.95. The IR spectra consisted of three sharp distinct bands at 1741, 1714, and 1660 cm^{-1} arising from carbonyl groups and showed the absence of cyanogroup of ethyl cyanoacetate. The proton-decoupled ^{13}C NMR spectrum of **4b** showed 18 distinctive resonances in agreement with the proposed structure.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 2. The reaction occurs via an initial formation of alkyl cyano-(1,3-dioxoindan-2-ylidene)acetate **5** from the condensation of ninhydrin and alkyl cyanoacetate which suffers nucleophilic attack followed by the loss of hydrogen cyanide to give aminoketone intermediate **6**. The intermediate **6** then undergoes cyclization to afford the product **4**. It is noticeable that this type of hydrogen cyanide loss is well precedenced [6]. In the case of the aminoketone **6**, cyclization is promoted because of aromatization of the product **4**.

The noteworthy feature of the ^1H NMR spectrum of **4a** is two separate signals for methylene of ester group. The ^1H NMR spectrum of **4a** in DMSO-d_6 at 25°C showed two distinct multiplets (two broad doublets of quartets) which coalesced near 318 K and appeared as a fairly sharp symmetrical quartet resonance at 348 K. This dynamic NMR effect is interpreted in terms of restricted rotation around the bond between condensed pyrido[2,3-*d*]pyrimidinedione core and CO_2Et group.

Although an expensive line shape analysis in relation to the dynamic NMR effect observed for **4a** was not undertaken in the present work, the variable temperature spectra allowed the calculation of the free energy barrier (if not the enthalpy or entropy of activation) for the dynamic NMR process in **4a**. From coalescence of the signals attributed to the methylene of ester group and using the expression $k = \pi\Delta\upsilon/\sqrt{2}$, we calculated that the first-order rate constant (k) for the dynamic NMR effect in **4a** to be 66.6 s^{-1} at 318 K. An application of the absolute rate theory with a transmission coefficient of 1 gives a free-energy of activation ($AG^{\#}$) of 14 ± 2 kJ mol^{-1} for **4a**, where all known sources of errors are estimated and included [7].

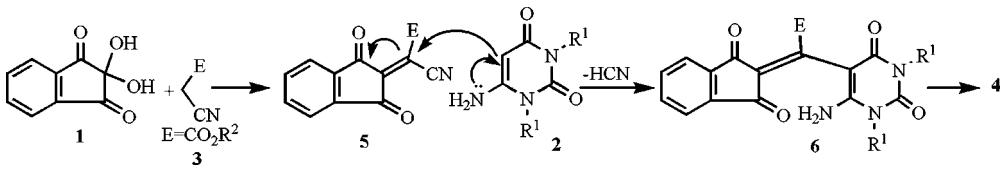
In conclusion, we have developed a novel and convenient one-pot condensation reaction for preparation of some new condensed pyrido[2,3-*d*]-pyrimidine(1*H*,3*H*)-2,4-diones under mild conditions and in good yields, utilizing in situ generation of aminoketone **6**.

EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomen FT-IR-MB 100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer. Elemental analysis for C, H, and N were performed using a Heraus CHN rapid analyzer. Chemicals were obtained from Merck and Fluka and used without further purification.

Synthesis of **4a** *as a General Procedure*

A magnetically stirred solution of ninhydrin **1** (0.178 g, 1 mmol), 6-amino-1,3-dimethylpyrimidine-2,4-dione **2a** (0.155 g, 1 mmol), and ethyl cyanoacetate **3a** (0.113 mL, 1 mmol) in ethanol (10 mL) was refluxed for 2 h. The reaction mixture was filtered and washed with hot ethanol (2×10 mL) to afford pure product **4a**.



SCHEME 2

*Methyl 1,3-Dimethyl-1H-inden-[2′,1′:5,6]-pyrido-[2,3-d]pyrimidine-2,4,6-trione-5-carboxylate (**4a**).* Yield 80%, mp 290°C (dec.), IR (KBr) υ: 1740, 1717, 1705, 1665 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.49 (3H, t, $J = 6.0$ Hz, O—CH_2CH_3), 3.46 (3H, s, NCH_3), 3.85 (3H, s, N—CH_3), 4.58 (1H, q, $J = 6.0$ Hz, O—CH_2Me), 4.69 (1H, q, $J = 6.0$ Hz, O—CH_2Me), 7.55–7.94 (4H, m, arom). ^{13}C NMR (DMSO-d_6) δ: 13.48, 28.08, 29.96, 62.26, 104.56, 118.98, 121.78, 123.67, 132.58, 134.77, 135.64, 139.73, 140.43, 150.18, 154.55, 159.13, 163.99, 168.54, 186.98. MS m/z (%): 365 (100) [M^+], 320 (95), 293 (97), 181 (100). Anal. Calcd for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.50; H, 4.10; N, 11.56.

*Ethyl 1,3-Dimethyl-1H-inden-[2′,1′:5,6]-pyrido[2,3-d]pyrimidine-2,4,6-trione-5-carboxylate (**4b**).* Light-yellow solid; mp 295°C (dec.), IR (KBr) υ: 1741, 1714, 1660, 1629 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.48 (3H, s, N—CH_3), 3.87 (3H, s, N—CH_3), 4.14 (3H, s, O—CH_3), 7.46–7.95 (4H, m, arom). ^{13}C NMR (DMSO-d_6) δ: 29.5, 32.6, 55.5, 108.7, 119.2, 121.0, 124.3, 130.2, 133.2, 134.5, 140.7, 143.4, 151.4, 159.8, 161.4, 163.0, 166.2, 187.3. MS m/z (%): 351 (M^+, 45), 320 (96), 292 (100). Anal. Calcd for $C_{18}H_{13}N_3O5$: C, 61.54; H, 3.73; N, 11.96. Found: C, 61.51; H, 3.73; N, 11.88.

*Methyl 1H-Inden-[2′,1′:5,6]-pyrido[2,3-d]pyrimidine-2,4,6-trione-5-carboxylate (**4c**).* Light-yellow solid; mp 302°C (dec.), IR (KBr) υ: 3475, 3130, 3020, 1746, 1716, 1672, 1655 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.32 (3H, broad, O—CH_2CH_3), 4.62 (2H, broad peak, O—CH_2Me), 7.46–7.79 (4H, m, arom), 12.00 (1H, broad peak, N—H), 12.31 (1H, broad peak, N—H). ^{13}C NMR (DMSO-d_6) δ: 13.63, 61.61, 104.48, 118.26, 121.84, 123.86, 133.19, 135.48, 135.76, 138.69, 140.48, 149.69, 157.29, 160.78, 163.74, 168.88, 187.49. MS m/z (%): 337 (M^+, 25), 292 (98), 265(100), 222 (98). Anal. Calcd for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.51; H, 3.29; N, 12.51.

*Ethyl 1H-Inden-[2′,1′:5,6]-pyrido[2,3-d]pyrimidine-2,4,6-trione-5-carboxylate (**4d**).* Light-yellow solid; mp 302°C (dec.), IR (KBr) υ: 3565, 3170, 3055, 1739, 1720, 1697 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.91 (3H, s, OCH_3), 7.64–7.79 (4H, m, arom), 11.75 (s, 1H, N—H), 12.46 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6) δ: 52.67, 104.55, 118.341, 121.86, 123.86, 133.20, 135.50, 136.07, 138.30, 140.47, 149.42, 157.28, 160.79, 164.35, 168.86, 187.46. MS m/z (%): 323 (M^+, 35), 292 (97), 264 (100). Anal. Calcd for $C_{16}H_9N_3O_5$: C, 59.45; H, 2.81; N, 13.00. Found: C, 59.41; H, 2.86; N, 13.07.

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