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Efficient one-pot synthesis of 2-oxo-1,9a-dihydro-2*H*-pyrido-[1,2-*a*]pyrimidine derivatives

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Abstract—Pyridines react smoothly with dialkyl acetylenedicarboxylates in the presence of isocyanates to produce dialkyl 2-oxo-1,9a-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine 3,4-dicarboxylates in excellent yields.

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity.[2,3] The interest in bicyclic 6–6 systems with one ring junction and one extra nitrogen atom, stems from the appearance of saturated and partially saturated pyrido[1,2-*a*]pyrimidine ring systems in many biologically active compounds and natural products,[3–9] some of which are key intermediates for the synthesis of rutaecarpine alkaloids, some have characteristic pharmacological properties such as analgesic antiallergic, antiasthmatic and antipsychotic agents, and some are neutral hydrogen chloride acceptors in organic synthesis.[3]

As part of our current studies on the development of new routes in heterocyclic synthesis,[10–14] in this letter, we wish to report that pyridines **1** undergo a smooth reaction with dialkyl acetylenedicarboxylates **2** in the presence of isocyanates **3** in dry dichloromethane at ambient temperature to produce functionalized 2-oxo-1,9a-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **4** in 85–98% yields (Scheme 1).

The reactions were carried out by first mixing the pyridine and the isocyanate and then the acetylenic ester was added slowly. The reactions proceeded spontaneously in CH_2Cl_2 and were complete within a few hours.[15]

The ^{1}H NMR spectrum of **4a** exhibited[15] two single sharp lines readily recognized as arising from methoxy protons (δ 3.82 and 3.97) along with four multiplets for the protons of an electron rich diene and an allylic proton as well as characteristic multiplets for the aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 16 distinct resonances in agreement with the structure of the product.

Although we have not established the mechanism of this reaction between pyridines and acetylenic esters in the presence of isocyanates in an experimental manner, a possible explanation is proposed in Scheme 2. The first step may involve addition of the pyridine to the acetylenic ester and formation of the 1:1 adduct **5**. Subsequent nucleophilic attack of the adduct to the isocyanate would yield bidentate anions **6** and **7**. The observed product is formed from the intramolecular addition of the nitrogen to the pyridinium moiety.

The ^{13}C NMR spectrum was used to distinguish the isolated product from the other possible structure **8**. Thus, the ^{13}C NMR spectrum of the isolated product exhibited a methine carbon resonance at about δ 70 ppm for $C_{9a}H$. The chemical shift for the methine carbon in **8** would be expected to appear at about δ 80 ppm.[16]

An alternative possible structure, 1-oxo-2,4a-dihydro-1*H*-pyrido[1,2-*c*]pyrimidine **9** (Scheme 3), which fits the analytical data, can be readily ruled out. This structure would be derived from initial addition of the pyridine to

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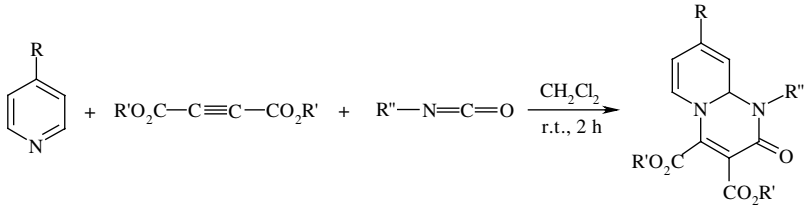
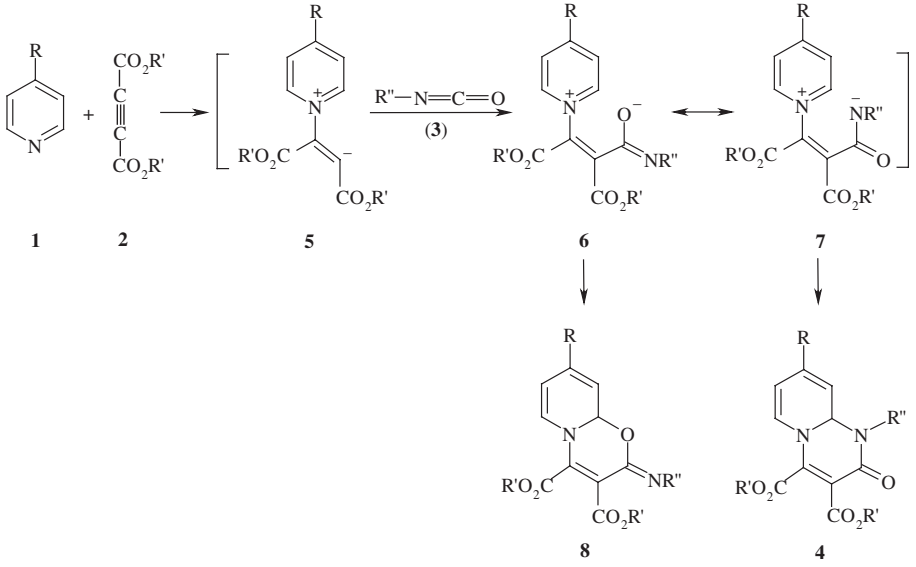


1 **2** **3** **4**

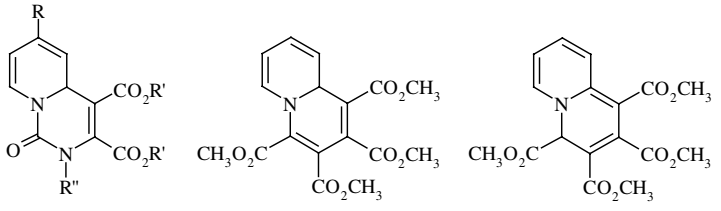
4	R	R'	R"	% Yield
a	H	CH_3	C_6H_5	98
b	H	C_2H_5	C_6H_5	95
c	CH_3	CH_3	C_6H_5	92
d	CH_3	C_2H_5	C_6H_5	85
e	H	CH_3	Cyclohexyl	90
f	H	CH_3	3,4-$Cl_2C_6H_3$	96
g	H	C_2H_5	Cyclohexyl	95
h	H	C_2H_5	3,4-$Cl_2C_6H_3$	95

Scheme 1.



1 **2** **5** **6** **7** **8** **4**

Scheme 2.



9 **10** **11**

Scheme 3.

the isocyanate, followed by cycloaddition of the adduct to the acetylenic ester. However, when pyridine and phenyl isocyanate were mixed under the reaction conditions, the reactants were recovered unchanged. Any product resulting from the nucleophilic attack of pyridine onto the isocyanate was not detected by ^{1}H and ^{13}C NMR spectroscopy. In addition, when pyridine, phenyl isocyanate and dimethyl acetylenedicarboxylate

were mixed all at once, 9a*H*-quinolizine **10** and its 4*H* isomer **11**[17] (Scheme 3) were formed under the reaction conditions whilst phenyl isocyanate was recovered unchanged. Consequently, the isolated product **4** is formed from the initial attack of the pyridine on the acetylenic ester.

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides an acceptable one-pot method for the preparation of functionalized 2-oxo-1,9a-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines.

Acknowledgements

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15. The procedure for the preparation of dimethyl 2-oxo-1-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine 3,4-dicarboxylate **4a** is described as an example. To a magnetically stirred solution of phenyl isocyanate (0.119 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in CH_2Cl_2 (2 mL) at −5 °C over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the residue was crystallized from 2:1 hexane–ethyl acetate. The product **4a** was obtained as yellow crystals, mp 117–119 °C, 0.33 g, yield 98%. IR (KBr) (ν_{max}/cm^{-1}): 1739, 1695, 1668, 1525, 1255. MS, *m*/*z* (%): 340 (M^+, 10). Anal. Calcd for $C_{18}H_{16}N_2O_5$ (340.34): C, 63.5; H, 4.7; N, 8.2. Found: C, 63.4; H, 4.8; N, 8.2. ^1H NMR (500 MHz, $CDCl_3$): δ 3.82 and 3.97 (6H, 2s, $2OCH_3$), 5.12 (1H, dd, *J* 10.1 Hz and *J* 3.1 Hz, CH), 5.39 (1H, dd, *J* 6.9 Hz and *J* 6.7 Hz, CH), 6.07 (1H, dd, *J* 8.3 Hz and *J* 7.9 Hz, CH), 6.15 (1H, dd, *J* 3.1 Hz and *J* 1.9 Hz, N–CH–N), 6.42 (1H, d, *J* 7.6 Hz, N–C*H*=CH), 7.11 (2H, d, *J* 7.5 Hz, *ortho* CH), 7.27 (1H, dt, *J* 2.4 Hz and *J* 7.1 Hz, *para* CH), 7.33 (2H, t, *J* 7.0 Hz, *meta* CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.23 and 53.62 ($2OCH_3$), 69.57 (N–CH–N), 104.39 (N–CH=*C*H), 105.09 (N–C=*C*), 115.75, 123.45, 123.71 and 127.87 (4CH), 128.65 (*ortho* CH), 129.67 (*meta* CH), 134.77 (*ipso* C), 149.22 (N–*C*=C), 158.89, 162.90 and 164.84 (3C=O).
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