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A new, one-pot, three-component synthesis of 4*H*-pyrido[1,2-*a*]-pyrimidines, 4*H*-pyrimido[1,2-*a*]pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines

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Abstract—A new, one-pot and three-component synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines, 4*H*-pyrimido[1,2-*a*]pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines is described. The reactive 1:1 zwitterionic intermediate, formed by the addition of isocyanides to dialkyl acetylenedicarboxylates, was trapped by *N*-(2-heteroaryl)amides to yield a ketenimine intermediate, which was cyclized and then rearranged under the reaction conditions to afford the title compounds under mild reaction conditions in good yields. Single-crystal X-ray analysis conclusively confirms the structure of the obtained bridgehead bicyclic 6–6 heterocyclic compounds.

1. Introduction

Multi-component reactions (MCRs) have become a significant part of today's arsenal of methods in combinatorial chemistry.[1] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[1b,c]

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity. The interest in bicyclic 6–6 systems stems from the occurrence of saturated and partially saturated pyrido[1,2-*a*]pyrimidines, pyrimido[1,2-*a*]pyrimidines, and pyrazino[1,2-*a*]pyrimidines in many biologically active compounds and natural products.[2–6]

To date, the most common synthetic methods reported for the preparation of pyrido[1,2-*a*]pyrimidine ring systems involve: (i) transformation of an existing heterocycle and (ii) cyclizations, classified on the basis of the number of ring atoms in each of the components being cyclized.[2,4]

There are several methods reported in the literature for the preparation of pyrimido[1,2-*a*]pyrimidine and pyrazino[1,2-*a*]pyrimidine ring system. The most common synthetic routes involve [3+3] ring closure of 2-aminopyrimidines and 2-aminopyrazines with a variety of bifunctional electrophiles.[3,7,8]

The diverse pharmacological activities of the three fused bicyclic 6–6 heterocycles encouraged us to develop a concise synthetic route to these heterocyclic compounds.

2. Results and discussion

As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds,[9] we report herein a simple synthesis of functionalized 4*H*-pyrido[1,2-*a*]pyrimidines,[4a] 4*H*-pyrimido[1,2-*a*]-pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines using simple starting materials from [1+2+3] atom fragments by formation of three bonds. Thus, a mixture of an isocyanide **1**, a dialkyl acetylenedicarboxylate **2**, and an *N*-(2-heteroaryl)amide **3** or **5** undergoes a smooth 1:1:1 addition reaction in dry CH_2Cl_2 at ambient temperature to produce 2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates **4a–j** in 83–92% yields (Scheme 1), 2-amino-4*H*-pyrimido[1,2-

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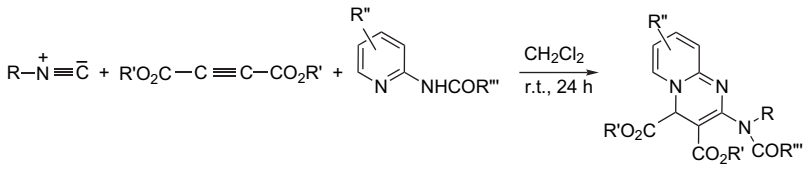


1 2 3 4

4	R	R'	R''	R'''	% Yield
a	Cyclohexyl	Me	H	CO_2Et	92
b	Cyclohexyl	Et	H	CO_2Et	88
c	Cyclohexyl	Me	7-Me	CO_2Et	90
d	Cyclohexyl	Et	7-Me	CO_2Et	85
e	Cyclohexyl	Me	H	OEt	83
f	^{t}Bu	Me	H	CO_2Et	89
g	^{t}Bu	Et	H	CO_2Et	85

Scheme 1.

a]pyrimidine-3,4-dicarboxylates, and 2-amino-4*H*-pyrazino[1,2-*a*]pyrimidine-3,4-dicarboxylates **6a–j** in 79–94% yields (Scheme 2).

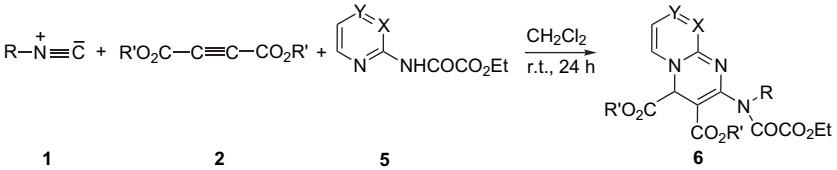
The one-pot three-component condensation reactions were carried out by first mixing acetylenic ester **2** and *N*-(2-heteroaryl)amide **3** or **5** in dry CH_2Cl_2. Then, a solution of isocyanide **1** in dry CH_2Cl_2 was added to the reaction mixture. The reaction proceeded smoothly at ambient temperature and was complete within 24 h to afford the corresponding pyrido[1,2-*a*]pyrimidines **4** or azino[1,2-*a*]pyrimidines **6**. The ^{1}H NMR spectra of the crude products clearly indicated the formation of fused system **4** or **6**. Any product other than **4** or **6** could not be detected by NMR spectroscopy.

The structures of the pyrido[1,2-*a*]pyrimidines **4a–g** were confirmed by IR, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at *m/z* 445, which was consistent with the 1:1:1 adduct of cyclohexyl isocyanide, dimethyl acetylenedicarboxylate, and ethyl 2-oxo-2-(2-pyridylamino)acetate. The ^{1}H NMR spectrum of **4a** exhibited three sharp singlets, arising from the two CH_3O (δ 3.64 and 3.69 ppm) and methine (δ 6.01 ppm) groups along with the characteristic signals with appropriate chemical shifts and coupling constants for the 16 protons of the ethoxy and cyclohexyl functions, as well as the characteristic multiplets for the four protons of the diene moiety of the pyridine ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 22 distinct resonances, in agreement with the proposed structure.

The isolated azino[1,2-*a*]pyrimidines **6a–g** were characterized on the basis of their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. The nature of these compounds as 1:1:1 adducts was apparent from the mass spectra, which displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectrum of **6a** consisted of multiplet signals for the 11 protons of the cyclohexyl ring and the five protons of the ethoxy function (δ 1.04–2.15 and 4.04–4.26 ppm). Three single sharp lines were observed for the two CH_3O (δ 3.70 and 3.74 ppm) and methine (δ 6.08 ppm) groups. Three characteristic doublet of doublets (δ 6.87, 7.90, and 8.76 ppm; J=6.6, 4.0, and 2.1 Hz) were seen for the three mutually coupling CHs in positions 6, 7, and 8 of the bicyclic ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 21 distinct resonances, in agreement with the suggested structure. Partial assignments of these resonances are given in Section 4.

Single-crystal X-ray analysis of **4a** conclusively confirmed the structure of the isolated products. An ORTEP diagram of **4a** is shown in Figure 1.[10]

A mechanistic rationalization for this reaction is provided in Scheme 3 (exemplified by **4**). On the basis of the well-established chemistry of isocyanides,[1b,c,11] it is reasonable to assume that the pyrido[1,2-*a*]pyrimidines **4** result from initial addition of isocyanide to acetylenic ester and subsequent protonation of the 1:1 zwitterionic adduct **7** by *N*-(2-pyridyl)-amide **3**, followed by conjugate addition of anion **9** from the pyridine nitrogen to the α,β-unsaturated nitrilium ion **8** to



1 2 5 6

6	R	R'	X	Y	% Yield
a	Cyclohexyl	Me	N	CH	94
b	Cyclohexyl	Et	N	CH	90
c	^{t}Bu	Me	N	CH	89
d	^{t}Bu	Et	N	CH	83
e	1,1,3,3-tetramethylbutyl	Et	N	CH	79
f	Cyclohexyl	Me	CH	N	91
g	Cyclohexyl	Et	CH	N	89

Scheme 2.