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Chemoselective synthesis of novel spiropyrano acenaphthylene derivatives *via* one-pot four-component reaction

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ABSTRACT

An efficient one-pot four-component condensation reaction of acenaphthoquinone, pyrazolones or barbituric acid and 1,1-bis(methylthio)-2-nitroethene and alkylamines in ethanol for the synthesis of novel spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazol]-2-one and spiro[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-trione is descibed. The significant features of this method include, readily available starting materials, operational simplicity, green solvent, catalyst-free condition, no column chromatographic purification and good to high yields.

Introduction

Multi-component reactions (MCRs) have emerged as a highly efficient synthetic tool in organic and medicinal chemistry because of their ability to synthesis Pharmaceutical compounds and their productivity, simple procedure, convergence, and facile execution.[1–4]

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The spiro functionality has been known for a long time to be present in phytochemicals either in alkaloids, lactones or terpenoids.[5] Biological activities of spiro compounds containing pyrans have also been proved. They also show good activity as hypertensive agents.[6] They have been the subject of great interest as potential novel analgesic agents.[7]

Pyrano[2,3-*c*]pyrazole derivatives are known for their wide range of biological activities such as antimicrobial,[8] insecticidal,[9] and anti-inflammatory.[10] Furthermore, compounds containing pyrano[2,3-*c*]pyrazole moiety have been reported to exhibit enzyme inhibition,[11] anticancer[12] and antifungal[13] activity apart from being significant intermediates for the construction of complex heterocycles.[14] In view of the biological significance, there has been extensive attention toward the development of synthetic routes for the synthesis of compounds containing pyrano[2,3-*c*]pyrazole core (Fig. 1).[15] Heterocyclic ketene aminals (HKAs), also referred to as ketene *N*-acetals, are powerful and versatile synthons and have made important intermediates for the construction of a wide variety for the synthesis of various types of heterocyclic compounds.[16–19]

A four-component reaction toward spiroacenaphthylene heterocycles is described herein *via* a catalyst free, one-pot, four-component condensation reaction.

Results and discussion

Initially, the four-component reaction of acenaphthoquinone **1**, pyrazolones or barbituric acids **2**, 1,1-bis(methylthio)-2-nitroethene **3** and alkylamines **4** in ethanol without catalyst at reflux for 3–4 h, afforded a series of spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives and spiro[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-trione derivatives **5** in 75–90% yields (Scheme 1).

We further were examined testing the effect of solvents and catalysts. Different solvents (solvent–water, EtOH) and also the effect of catalyst on the yield of product were examined to develop standard reaction condition and the results are summarized in Table 1. Water showed no superiority to EtOH (Table 1, entry 3) and the reaction proceeded with excellent yields when ethanol was used as the solvent. The optimized reaction conditions were then tested for library construction with acenaphthoquinone **1**, pyrazolone **2**, (*Z*)-*N*-methyl-1-(methylthio)-2-nitroethen-1-amine **3** and **4**. The effects of solvents and catalyst for this model reaction, and the results are summarized in (Table 1). When the same

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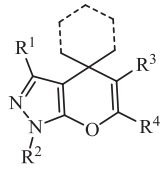
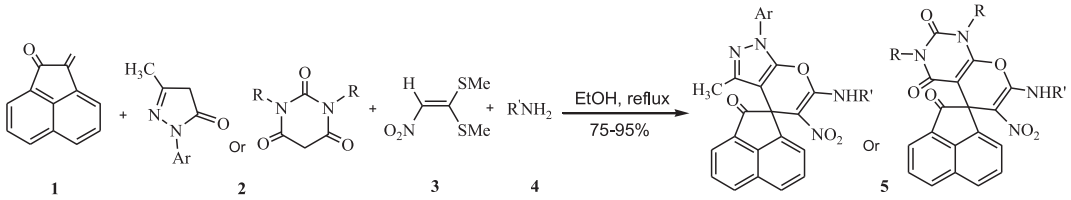


Fig. 1. Pyrano[2,3-*c*]pyrazole derivatives.



Scheme 1. Synthesis of spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazol]-2-one.

Table 1
Synthetic results of **5a** under different conditions.[a]

Entry	Solvent	Temperature (°C)	Catalyst (20%)	Time (h)	Isolated yield (%)[b]
1	**EtOH[c]**	**80**	**–**	**3.5**	**81**
2	EtOH	r.t.	–	8	30
3	H_2O	80	–	15	25
4	H_2O	r.t	–	8	30
5	EtOH[c]	80	Et_3N	3.5	70
6	**EtOH**	**80**	**SiO_2**	**3.5**	**90**
7	H_2O	80	Et_3N	12	35
8	EtOH	r.t.	Et_3N	12	10
9	H_2O	r.t.	Et_3N	12	40

[a] Compound **1** (1 mmol), **2** (1 mmol), and **3** and **4** (1 mmol), solvent 5 mL.
[b] Yield of isolated **5a**.

reaction was carried out in the presence of nano SiO_2 as catalyst, product **5a** was obtained in 90% yield (entry **6**, Table 1).

We explored the scope of this reaction by varying the structure of pyrazolones or barbituric acids **2**, and the primary amine **4** components. The reaction proceeds cleanly in the presence of alkyl amines (Table 2) to afford a series of spiro products **5** in 75–95% yields, whereas the reaction completely failed to occur in the cases of aromatic amines (aniline, *p*-toluidine, 4-nitroaniline).

The structure of compounds **5a–l** were elucidated from their mass, IR, and ^1H and ^{13}C NMR spectra (ESI).[20] The IR spectrum of **5** showed absorption bonds due to the NH group at 3432, and 3198 cm^{-1}. Stretching frequencies related to the C=O, C=C, and NO_2 functional groups appeared at 1730, 1652, 1469 and 1350 cm^{-1}, respectively. The ^1H NMR spectrum of **5a** exhibited a dublet recognized as arising from the NCH_3 group (δ = 3.12 ppm, $^3J_{HH}$ = 5.1 Hz) and a broad singlet due to a NH group (δ = 10.65 ppm), which exchanged with D_2O. The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. ^1H decoupled ^{13}C NMR spectrum showed 25 distinct signals in agreement with the proposed structure. Resonances due to spiro carbon, CH_3—Ph, C—$NHCH_3$, C—NO_2, and C=O appeared at δ = 54.3, 12.8, 28.3, 98.4 and 201.4, respectively.

A plausible mechanism of the reaction is depicted in Scheme 2. First, the reaction of 1,1-bis(methylthio)-2-nitroethylene **3** and alkylamine **4** produces the (*E*)-*N*-methyl-1-(alkylthio)-2-nitroethen-1-amine **6**. In the next step the addition of acenaphthoquinone **1**, pyrazolone or barbituric acid to the reaction pot changed the color of reaction mixture to white due to the formation of

Table 2
Product **5a–5l**.[a]

Entry	Product	Ar	R′	R	Time (h)	Yields (%)[b]	m.p. °C (dec.)
1	**5a**	2-ClC_6H_4	CH_3	–	3.5	83	262–263
2	**5b**	3-ClC_6H_4	CH_3	–	3.5	87	309–310
3	**5c**	C_6H_5	CH_3	–	3.5	81	303–304
4	**5d**	–	CH_3	CH_3	3.5	90	317–318
5	**5e**	–	CH_3	H	3.5	85	330–331
6	**5f**	–	CH_2CH_3	H	3.5 + 5	95	289–290
7	**5g**	C_6H_5	$CH(CH_3)_2$	–	3.5 + 5	75	290–291
8	**5h**	C_6H_5	CH_2CH_3	–	3.5 + 5	89	280–281
9	**5i**	2-ClC_6H_4	$CH(CH_3)_2$	–	3.5 + 5	81	268–269
10	**5j**	3-ClC_6H_4	$CH(CH_3)_2$	–	3.5 + 5	82	276–277
11	**5k**	2-ClC_6H_4	CH_2CH_3	–	3.5 + 5	78	262–263
12	**5l**	3-ClC_6H_4	CH_2CH_3	–	3.5 + 5	75	251–252

[a] Acenaphthoquinone **1** (1 mmol), CH acids **2** (1 mmol), 1,1-bis(methylthio)-2-nitroethene **3** (1 mmol), and alkylamine **4** (1 mmol) were used in ethanol at reflux.
[b] Isolated yield based on barbituric acid and pyrazolones.