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JSCS–3924 *Short communication*

SHORT COMMUNICATION

Synthesis and characterization of a series of 1,3,5-trisubstituted-2-pyrazolines derivatives using methanoic acid under thermal condition

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Abstract: An efficient and practical synthesis of 1,3,5-trisubstituted 2-pyrazoline structures was achieved through cyclization of phenylhydrazine with α,β--unsaturated ketones (chalcones) using methanoic acid (formic acid) as catalyst under thermal condition.

Keywords: 1,3,5-trisubstituted-2-pyrazoline; phenylhydrazine; chalcone; methanoic acid; heterocyclic synthesis.

INTRODUCTION

Chalcones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities and are well-known intermediates for the synthesis of various heterocycles. Chalcones are useful synthons in the synthesis of a large number of bioactive molecules, such as pyrazolines and isoxazoles that are well-known nitrogen-containing heterocyclic compounds.[1–5]

The discovery of this class of compounds provides an outstanding case history of modern drug development and also emphasizes the unpredictability of biological activity from structural modification of a prototype drug molecule. Considerable interest has been focused on the pyrazoline structure, which is known to possess a broad spectrum of biological activities, such as antitumor,[6] immunosuppressive,[7] antibacterial,[8] anti-inflammatory,[9] anticancer,[10] antidiabetic[11] and antidepressant.[12] Thus, the synthesis of the 1,3,5-trisubstituted 2-pyrazolines moiety is always a great challenge.

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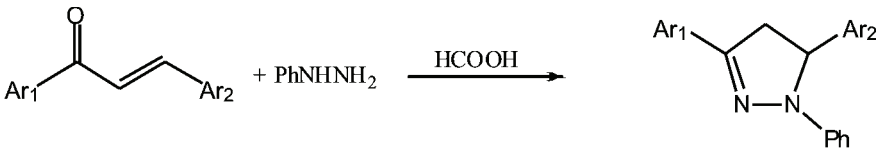
Among various pyrazolines derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type of compounds. Various procedures have been developed for the synthesis of pyrazolines.[13–15] After the pioneering work of Fischer and Knoevenagel in the 19th century, the reaction of *α*,*β*-unsaturated aldehydes and ketones with phenylhydrazine in acetic acid under reflux became one of the most popular methods for the preparation of 2-pyrazolines.[16–18]

In continuation of our research on the synthesis of 1,3,5-trisubstituted-2-pyrazolines,[19–21] a facile synthesis of a range of 1,3,5-trisubstituted-2-pyrazolines from *α*,*β*-unsaturated ketones (chalcones) and phenylhydrazine in the presence of methanoic acid is described herein (Scheme 1).



Scheme 1. General reaction for the preparation of 1,3,5-trisubstituted-2-pyrazolines.

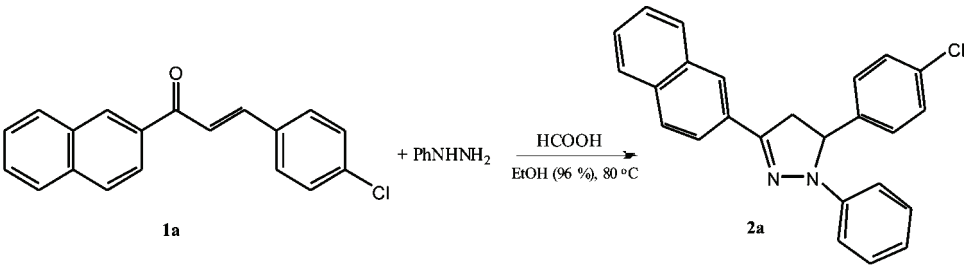
RESULTS AND DISCUSSIONS

Methanoic acid (HCOOH, pK_a = 3.744) is a versatile organic compound. It is well known as a natural product and as a one-carbon source in organic chemistry.[22] Under appropriate conditions, it decomposes to carbon dioxide and hydrogen and the generated hydrogen can be used under transfer hydrogenation conditions for the reduction of a wide variety of functional groups.[23–25] Furthermore, methanoic acid has found extensive use as an oxidizing agent.[26]

First, 3-(4-chlorophenyl)-1-(2-naphthyl)prop-2-en-1-one (1.0 mmol) was chosen as the trial substance for reaction with phenylhydrazine (2.0 mmol) in the presence of methanoic acid. Different solvents were screened for the synthesis of 2-pyrazolines and the results are summarized in Table I, from which it can be seen that EtOH was the best solvent in terms of reaction time and yield (Entry 1). Then, the effect of the amount of the catalyst, methanoic acid, on the yield and time of the same reaction was investigated. In the absence of catalyst, no product was obtained after 2 h (Table I, Entry 4). It was found that 2.5 ml of the catalyst was sufficient to mediate the reaction towards the formation of the 1,3,5-trisubstituted-2-pyrazoline in terms of time and yield (Table I, Entry 5).

Having established the reaction conditions, various chalcones (**1a**–**q**), prepared by Claisen–Schmidt condensation of aromatic ketones with aromatic aldehydes, were treated with phenylhydrazine in the presence of methanoic acid to investigate the scope of the reaction. The obtained 1,3,5-trisubstituted-2-pyrazolines (**2a**–**q**) are presented in Table II, together with their melting points and the reaction times and yields.

TABLE 1.Optimization of the reaction conditions



1a 2a

Entry	Catalyst amount/ ml	Solvent	Time/ min	Yield[a]/ %
1	1	EtOH	30	80
2	1	MeOH	45	60
3	1	CH3CN	50	50
4	–	EtOH	120	–
5	2.5	EtOH	15	90
6	3.5	EtOH	15	62
7	4.5	EtOH	35	48

[a]Isolated yield

TABLE II. Synthesis of 1,3,5-trisubstituted 2-pyrazolines in the presence of methanoic acid

Product	Ar1	Ar2	Time/ min	Yield[a]/ %	M.p./ °C	
					Found	Reported[b]
2a	2-naphthyl	4-ClC_6H_4	15	90	128–130	129–130
2b	2-naphthyl	2-ClC_6H_4	10	80	123–125	124–126
2c	C_6H_5	4-$CH_3C_6H_4$	15	90	130–132	128–130
2d	C_6H_5	2-ClC_6H_4	15	72	134–136	134–135
2e	4-$MeOC_6H_4$	C_6H_5	15	80	139–140	134–136
2f	C_6H_5	4-$MeOC_6H_4$	15	75	108–110	110–112
2g	C_6H_5	C_6H_5	25	82	132–134	134–135
2h	4-ClC_6H_4	C_6H_5	15	84	140–142	143–145
2i	2-naphthyl	3-$CH_3C_6H_4$	15	90	150–151	152–154
2j	2-naphthyl	2-$CH_3C_6H_4$	20	92	170–172	169–171
2k	C_6H_5	3-BrC_6H_4	20	88	134–136	135–136
2l	4-$MeOC_6H_4$	2-ClC_6H_4	15	82	149–150	148–150
2m	2-naphthyl	4-$MeOC_6H_4$	20	90	134–136	135–136
2n	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$	25	80	125–126	124–126
2o	4-$MeOC_6H_4$	2-$CH_3C_6H_4$	25	80	90–92	88–90
2p	4-$MeOC_6H_4$	3-$CH_3C_6H_4$	25	74	110–112	112–114
2q	3-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$	35	80	142–144	New

[a]Isolated yield; [b]literature data[17,19-21]

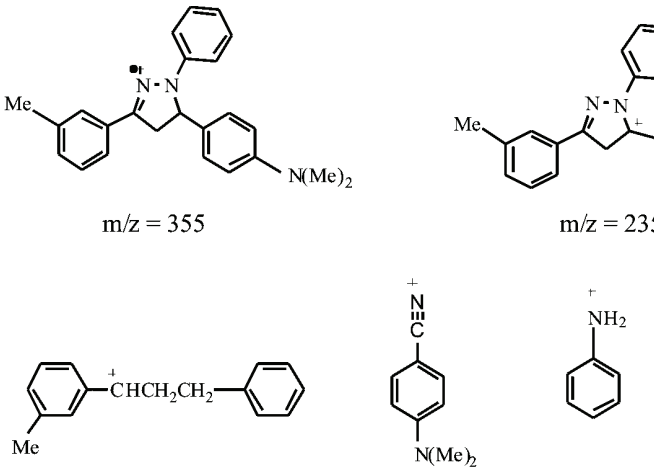
All the isolated products were characterized based on their physical properties and IR, ^{1}H-NMR and mass spectral data, and by direct comparison with authentic materials. All the synthesized compounds gave the expected spectral

data. As a representative product, the spectroscopic data for 5-[4-(dimethylamino)phenyl]-3-(3-methylphenyl)-1-phenyl-2-pyrazoline (**2q**) are given below.

IR (KBr, cm^{-1}): 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of pyrazoline ring), 1595, 1520, 1499 (C=C stretching of aromatic ring), 1219 (C–N stretching of pyrazoline ring), 745 (C–H bending).

^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 2.28 (3H, *s*, CH_3), 2.81 (6H, *s*, $N(CH_3)_2$), 3.05 (1H, *dd*, $-CH_{2pyraz.}$), 3.63 (1H, *dd*, $-CH_{2pyraz.}$), 5.05 (1H, *dd*, $-CH_{pyraz.}$), 6.62–7.48 (13H, *m*, Ar-H).

MS (m/z, *(relative abundance, %)*): 355 (M^+, 82.35), 235 (M–120, 16.87), 208 (M–27), 20.58), 147 (M–61, 55.88), 91 (M–56, 76.47) (see Scheme 2).

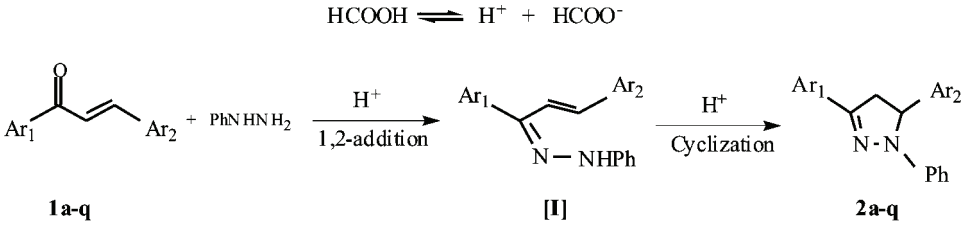


Scheme 2.

Methanoic acid is a source of H^+, the following sequence of reaction appears to afford a satisfactory explanation of the mode of formation of the products (Scheme 3). This reaction involves the initial formation of an arylhydrazone (**I**) with the subsequent attack of the nitrogen on the carbon-carbon double bond.[17,19–21]

EXPERIMENTAL

The IR spectra as KBr discs were recorded on a Shimadzu 435-U-04 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Jeol FT NMR 90 MHz spectrometer in $CDCl_3$ with TMS as the internal reference. The melting points were determined on a Stuart SMP3 apparatus and are uncorrected. Mass spectra were recorded on a GCMS--QP1100EX spectrometer.



Scheme 3.

*General procedure for the synthesis of 1,3,5-trisubstituted-2-pyrazolines (**2a**–**q**)*

To a stirred solution of chalcone (**1a**–**q**, 1.0 mmol) in 10 ml EtOH (96 %) was added phenylhydrazine (2.0 mmol) and methanoic acid (2.5 ml) at room temperature. The reaction mixture was heated to reflux for an appropriate time (see Table II). The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and residue recrystalized from EtOH (2 × 5 ml) to afford the pure products (**2a**–**q**).

CONCLUSIONS

In conclusion, a rapid, high yield, simple, practical, economic, readily available system, and convenient procedure for the synthesis of 1,3,5-trisubstituted-2--pyrazolines, which compares well with the similar acetic acid system under the same conditions, has been developed.

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ИЗВОД

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА 1,3,5-ТРИСУПСТИТУИСАНИХ-2-ПИРАЗОЛИН ДЕРИВАТА СА МЕТАНСКОМ КИСЕЛИНОМ КАО КАТАЛИЗАТОРОМ УЗ ЗАГРЕВАЊЕ

BEHROOZ MALEKI[1], DAVOOD AZARIFAR[2], MONA KHODAVERDIAN MOGHADDAM[1], SEYEDEH FATEMEH HOJATI[1], MOSTAFA GHOLIZADEH[1] и HAFEZEH SALEHABADI[1]

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Ефикасна и практична синтеза 1,3,5-трисупституисаних 2-пиразолин структура изведена је циклизацијом фенилхидразина са α,β-незасићеним кетонима (халконима) са метанском (мрављом) киселином као катализатором уз загревање.

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