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Original article

An efficient and facile synthesis of novel 1,2,3-triazolyl-*N*-acylpyrazoline hybrids

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ABSTRACT

An efficient and facile synthesis of a library of hitherto novel 1,2,3-triazolyl-*N*-acetyl/*N*-propionylpyrazoline hybrids (16 examples) in excellent yields (90%–96%) has been accomplished from easily accessible 1,2,3-triazolyl chalcone precursors.

1. Introduction

Recently, considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. They possess anti-microbial [1], anti-fungal [2], anti-depressant [3], anti-convulsant [4], anti-inflammatory [5], *etc.* properties. Moreover, *N*-acetyl pyrazoline derivatives exhibit important pharmaceutical profiles [6–8]. Hence, the pyrazoline framework represents an interesting template for combinatorial [9] as well as medicinal chemistry [10,11]. On the other hand, 1,2,3-triazoles have received much attention due to their interesting bioactivity profile such as anti-biotic, anti-fungal [12], anti-cancer [13], anti-HIV [14], anti-microbial [15], *etc.* properties. Also, they serve as potential chemotherapeutic agents for various diseases [16].

In connection with the above and in continuation of our earlier work on environmentally benign, green synthesis of 1,2,3-triazolyl chalcone hybrids [17], we decided to attempt the synthesis of molecules containing both of the two pharmacologically active moieties mentioned above in a single frame. Thus, we disclose the synthesis of 1,2,3-triazolyl-*N*-acylpyrazoline hybrids from easily accessible 1,2,3-triazolyl chalcones, the details of which are presented *vide infra*.

Chalcones, belonging to the flavonoids family, are convenient synthons for the synthesis of five [18], six [19] and seven membered [20] heterocyclic compounds. With regard to pyrazoline derivatives, several methods have been employed for their synthesis, including the condensation of chalcones with hydrazine, hydrazine derivatives [21–24] and thiosemicarbazide [25] under acidic [21,22] or basic [25] conditions, and the cycloaddition of nitrilimines, generated *in situ* from the corresponding hydrazonoyl halides by the action of a suitable base, to carbon-carbon double bonds of a dipolarophile [26–29]. Hence, considerable interest has been focused on the synthesis of pyrazolines from chalcones.

2. Experimental

Typical procedure: To a solution of (*E*)-1-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-(4-methylphenyl)prop-2-en-1-one [18] (**1e**, 1.0 equiv.) and hydrazine hydrate (2.0 equiv.) in acetic acid (5 mL) was refluxed for 3 h. Then, the reaction mixture was poured onto ice-water to afford the 1,2,3-triazolyl-*N*-acetylpyrazoline hybrid (**2e**) in 96% yield as a white solid, which was filtered and recrystallized from ethanol.

1-(3-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**2e**): Mp: 150–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11–7.37 (m, 9H, ArH), 5.54 (s, 2H, NCH_2), 5.50 (dd, 1H, J = 4.8 & 12.0 Hz, CH), 3.87(dd, 1H, J = 12.0 & 18.6 Hz, CH_2), 3.44 (dd, 1H, J = 4.8 & 18.6 Hz, CH_2), 2.51(s, 3H, $COCH_3$), 2.32 (s, 3H, CH_3), 2.29 (s, 3H, $ArCH_3$); ^{13}C NMR

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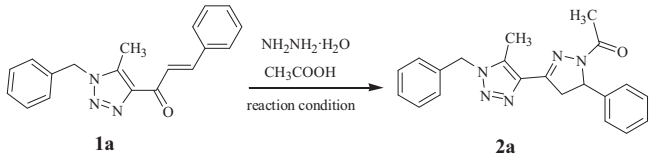


Scheme 1. Optimization for the synthesis of 1,2,3-triazole-*N*-acetylpyrzoline hybrid (**3a**).

(75 MHz, $CDCl_3$): δ 168.46, 149.47, 138.68, 138.24, 137.19, 134.25, 132.80, 129.41, 129.08, 128.53, 127.25, 125.65, 58.69, 51.95, 43.25, 21.79, 21.00, 9.41; Mass (ES/MS): *m/z* 396.58 $[M+Na]^+$; Anal. Calcd. for $C_{22}H_{23}N_5O$: C 70.76, H 6.21, N 18.75. Found: C 70.70, H 6.22, N 18.78.

3. Results and discussion

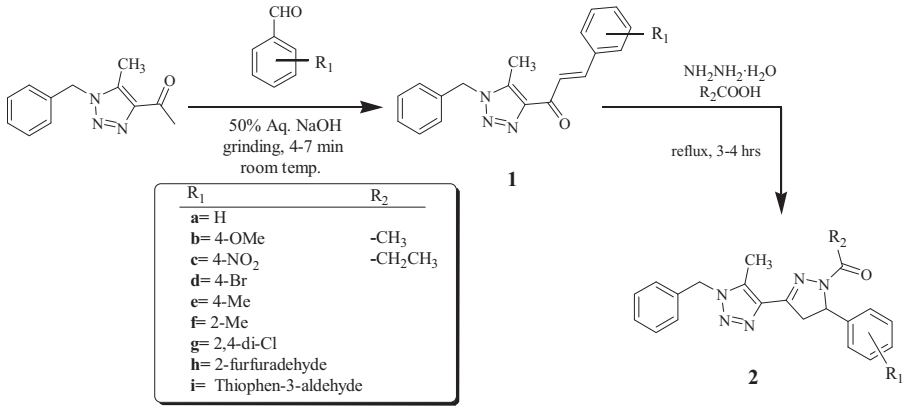
Perusal of literature indicates a lack of reports on the synthesis of *N*-acylpyrazolines linked with a 1,2,3-triazole core. In this regard, we herein report synthesis of novel 1,2,3-triazolyl-*N*-acylpyrazoline hybrids in a facile and efficient manner starting from chalcones [17].

Table 1
Optimization for the synthesis of 1,2,3-triazole-*N*-acetylpyrzoline hybrid (**3a**).

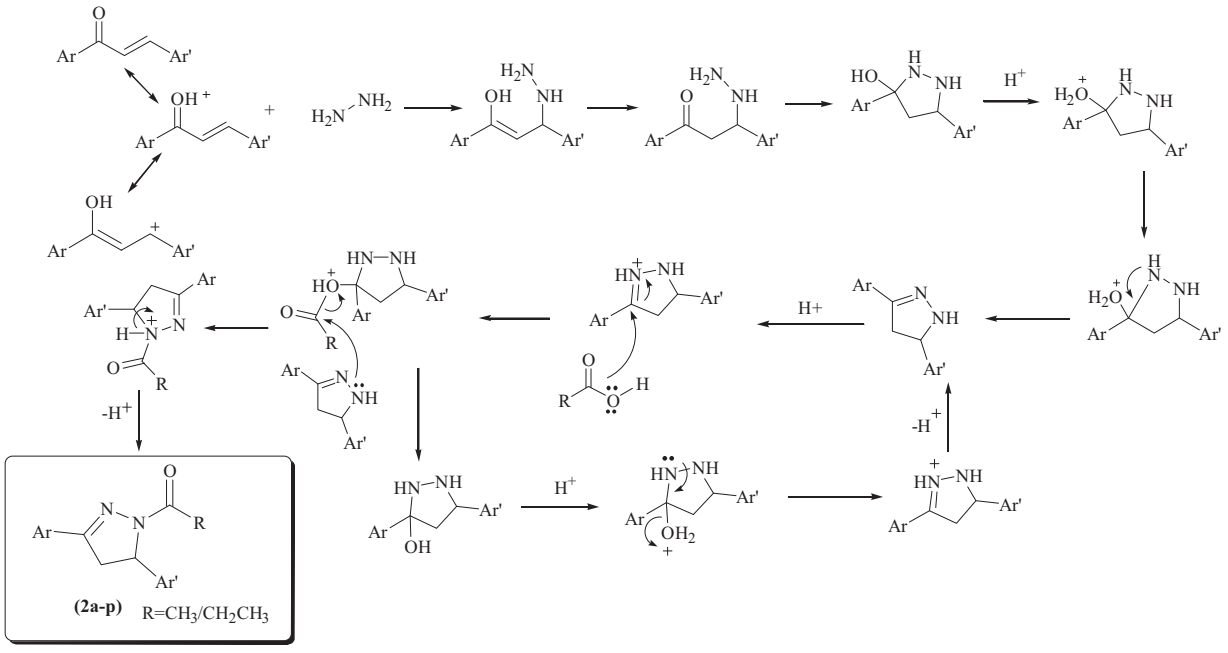
Chalcone	Reaction condition				
	Conventional heating		MW-irradiation		
	Time (h)	Yield (%)	Time (min)	Temp. (°C)	Yield (%)
1a	1	55	10	100	55
1a	2	75	20	100	60
1a	2.5	88	30	100	60
1a	3	95	20	130	60
1a	3.5	95			

For the purpose of optimization, synthesis of *N*-acetylpyrazoline (**3a**) was attempted (Scheme 1) under different conditions *viz.* (i) reaction through conventional heating (ii) reaction under microwave irradiation. The details are presented below.

A mixture of 1,2,3-triazolyl chalcone (**1a**, 1.0 equiv.) and hydrazine hydrate (2.0 equiv.) in acetic acid was conventionally heated to reflux. It was noted that the yield of *N*-acetylpyrazoline (**2a**) was increased and reached 95% in three hours. However, by changing the source of heating to microwave irradiation, a comparable yield of the product could not be obtained



Scheme 2. Synthesis of 1,2,3-triazolyl-*N*-acetyl/*N*-propionylpyrzolines (**2**).



Scheme 3. A feasible mechanism for *N*-acylatedpyrazolines.

Table 2
Synthesis of 1,2,3-triazolyl-*N*-acetyl/*N*-propionylpyrazoline hybrids (**2a–p**).

Entry	Chalcones (**1a-i**)	R_2	Time[a] (h)	Product	Yield (%)
1	**1a**	CH_3	3	**2a**	95
2	**1b**	CH_3	3	**2b**	96
3	**1c**	CH_3	3.5	**2c**	94
4	**1d**	CH_3	3	**2d**	95
5	**1e**	CH_3	3	**2e**	96
6	**1f**	CH_3	4	**2f**	93
7	**1g**	CH_3	4	**2g**	93
8	**1h**	CH_3	3.5	**2h**	94
9	**1i**	CH_3	3.5	**2i**	95
10	**1a**	CH_3CH_2	4	**2j**	92
11	**1c**	CH_3CH_2	4	**2k**	92
12	**1d**	CH_3CH_2	3.5	**2l**	92
13	**1e**	CH_3CH_2	4	**2m**	93
14	**1g**	CH_3CH_2	4	**2n**	90
15	**1h**	CH_3CH_2	3	**2o**	91
16	**1i**	CH_3CH_2	3	**2p**	90

[a] Reaction times are reported based on TLC monitoring.

(Table 1). Thus, conventional heating was found to be the best methodology for the target compounds.

Following optimization, the broad scope of the present protocol was established *via* the synthesis of a library of novel 1,2,3-triazolyl-*N*-acetyl/*N*-propionylpyrazoline hybrids (**2a–p**, Scheme 2) in excellent yields (90%–96%, Table 2), and it was noted that the reaction involving acids with long alkyl chains such as butyric acid, pentanoic acid, *etc.* was not satisfactory.

All the synthesized compounds were completely characterized by IR, NMR (1D & 2D) and mass spectral techniques. The feasible mechanism is presented vide Scheme 3.

4. Conclusion

In conclusion, we have achieved an efficient and facile synthesis of a library of hitherto novel 1,2,3-triazolyl-*N*-acetyl/*N*-propionylpyrazoline hybrids in excellent yields *via* easily accessible chalcones.

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References

[1] M. Alam, S.A.A. Nami, M. Parveen, et al., Microwave assisted synthesis and *in silico* screening of steroidal pyrazolines, Chin. Chem. Lett. 23 (2012) 1039–1042.
[2] S.S. Korgaokar, P.H. Patil, M.T. Shah, H.H. Parekh, Studies on pyrazolines: preparation and antimicrobial activity of 3-(3′(p-chlorophenylsulphonamidophenyl)-5-aryl-acetylpyrazolines, Indian J. Pharm. Sci. 58 (1996) 222–225.
[3] P.Y. Rajendra, R.A. Lakshmana, et al., Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines, Bioorg. Med. Chem. Lett. 15 (2005) 5030–5034.
[4] Z. Ozdemir, H.B. Kandilici, et al., Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives, Eur. J. Med. Chem. 42 (2007) 373–379.
[5] R.H. Udupi, A.S. Kushnoor, A.R. Bhat, Synthesis and biological evaluation of certain pyrazoline derivative of 2-(6-methoxynaphthyl)-propionic acid, Indian J. Heterocycl. Chem. 8 (1998) 63–66.
[6] A.K. Rana, S.B. Lade, S. Sorathia, et al., Synthesis, characterization and antimicrobial evaluation of some new *N*-acetyl pyrazoline derivatives from substituted furan-2-carbaldehyde, Der Chem. Sin. 4 (2012) 965–969.
[7] A.M. Fahmy, K.M. Hassa, A.A. Khalaf, R.A. Ahmed, Synthesis of some new beta-lactams, 4-thiazolidinones and pyrazolines, Indian J. Chem. 26 (1987) 884–887.
[8] B. Holla, P.M. Shivarama, M.K. Akberali, Shivananda, Studies on arylfuran derivatives: part X. Synthesis and antibacterial properties of arylfuryl-delta (2)-pyrazolines, Farmaco 55 (2000) 256–263.
[9] P. Brooking, A. Doran, P. Grimsey, et al., Split–Split. A multiple synthesiser approach to efficient automated parallel synthesis, Tetrahedron Lett. 40 (1999) 1405–1408.
[10] J. Regan, S. Breitfelder, P. Cirillo, T. Gilmore, et al., Pyrazole urea-based inhibitors of p38 MAP kinase: from lead compound to clinical candidate, J. Med. Chem. 45 (2002) 2994–3008.
[11] P. Pevarello, M.G. Brasca, R. Amici, P.G. Orsini, et al., 3-Aminopyrazole inhibitors of CDK_2/cyclin A as antitumor agents. 1. Lead finding, J. Med. Chem. 47 (2004) 3367–3380.
[12] X.L. Wang, K. Wan, C.H. Zhou, Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities, Eur. J. Med. Chem. 45 (2010) 4631–4639.
[13] W.T. Li, W.H. Wu, C.H. Tang, R. Tai, S.T. Chen, One-pot tandem copper-catalyzed library synthesis of 1-thiazolyl-1,2,3-triazoles as anticancer agents, ACS Comb. Sci. 13 (2011) 72–78.
[14] R. Alvarez, S. Velazquez, A. San-Felix, et al., 1,2,3-Triazole-[2′,5′-bis-O-(tert-butyldimethylsilyl-b-D-ribofuranosyl]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide) (TSAO) analogues. Synthesis and anti-HIV-1 activity, J. Med. Chem. 37 (1994) 4185–4194.
[15] Xu Zhao, Bo Wei Lu, Jun Rui Lu, et al., Design, synthesis and antimicrobial activities of 1,2,3-triazole derivatives, Chin. Chem. Lett. 23 (2012) 933–935.
[16] S. Wang, Q. Wang, Y. Wang, L. Liu, et al., Novel anthraquinone derivatives: synthesis via click chemistry approach and their induction of apoptosis in BGC gastric cancer cells via reactive oxygen species (ROS)-dependent mitochondrial pathway, Bioorg. Med. Chem. Lett. 18 (2008) 6505–6508.
[17] P. Shanmugavelan, M. Sathishkumar, S. Nagarajan, et al., A facile synthesis of 1, 2,3-triazolyl indole hybrids via $SbCl_3$-catalysed Michael addition of indoles to 1,2,3-triazolyl chalcones, J. Chem. Sci. 124 (2012) 941–950.
[18] B.J. Gaede, L.L. Mc Dermott, Novel perfluoroalkyl-substituted pyrazoles. 1. Hydroxypyrazoles, J. Heterocycl. Chem. 30 (1993) 49–54.
[19] K. Shibata, I. Katsuyama, H. Izoe, et al., Synthesis of 4,6-di substituted 2-methyl pyridines and their 3-carboxamides, J. Heterocycl. Chem. 30 (1993) 277–281.
[20] X. Jiaxi, C. Wang, Q. Zhang, Synthesis of 1-3,3a,5-tetraaryl-3a,4,5,6-tetrahydro-3H-1,2,4-trizolo[4,3-a][1,5] benzodiazepines, Heteroatom Chem. 6 (2001) 557–559.
[21] D. Azarifar, H. Ghasemnejad, Microwave-assisted synthesis of some 3,5-arylated 2-pyrazolines, Molecules 8 (2003) 642–648.
[22] D. Azarifar, M. Shaebanzadeh, Synthesis and characterization of new 3,5-dinaphthyl substituted 2-pyrazolines and study of their antimicrobial activity, Molecules 7 (2002) 885–895.
[23] M.A. Ali, M.S.A.A. Siddiqui, Synthesis, structural activity relationship and antitubercular activity of novel pyrazoline derivatives, Eur. J. Med. Chem. 42 (2007) 268–275.
[24] M. Amir, H. Kumar, S.A. Khan, Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents, Bioorg. Med. Chem. Lett. 18 (2008) 918–922.
[25] M. Kidwai, S. Kukreja, R. Thakur, K_2CO_3-mediated regioselective synthesis of isoxazoles and pyrazolines, Lett. Org. Chem. 3 (2006) 135–139.
[26] H.M. Hassaneen, A.S. Shawali, N.M. Elwaln, et al., Synthesis and cycloaddition reactions of *C*-(2-naphthoyl)-*N*-arylmethanohydrazonylpyridinium bromides, Arch. Pharm. Res. 15 (1992) 292–297.
[27] H.M. Hassaneen, R.H. Hilal, N.M. Elwan, et al., The regioselectivity in the formation of pyrazolines and pyrazoles from nitrilimines, Heterocycl. Chem. 21 (1984) 1013–1016.
[28] H.M. Hassaneen, H.A.H. Mousa, A.S. Shawali, Chemistry of C-heteroarylnitrilimines. Synthesis and cycloaddition reactions of *N*-phenyl-*C*-(2-thienyl)nitrilimine, J. Heterocycl. Chem. 24 (1987) 1665–1668.
[29] H.M. Hassaneen, H.A.H. Mousa, N.M. Abed, A.S. Shawali, Chemistry of *C*-heteroarylhydrazidoyl halides. Synthesis and reactions of *N*-(*p*-Nitrophenyl)-*C*-(2-thienyl)-formohydrazidoyl halides, Heterocycles 27 (1988) 695–706.