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Synthesis of *N*-Acyl Triazolyl-Pyrazolines *via*. Acylation Initiated by the Hydrazone Moiety with Carboxylic Acids

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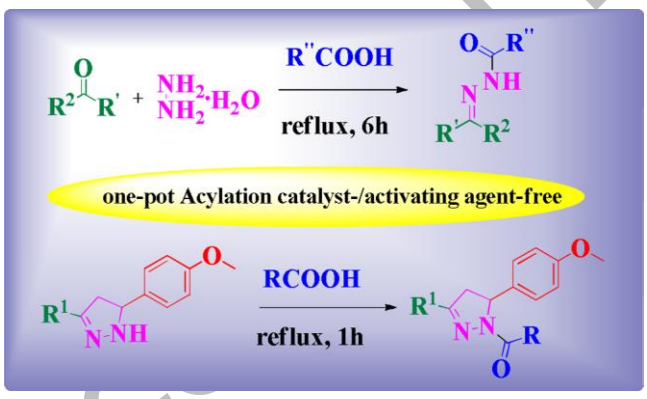
Abstract

An efficient synthesis of *N*-acyl/*N*-substituted acyl pyrazolines and their triazole hybrids have been accomplished *via* acylation of pyrazolines and pyrazoline-triazole hybrids with carboxylic acids and/or substituted carboxylic acids in the absence of activating agents/catalysts. In the present study, a mechanism envisaging the *insitu* generation of a new transient acylating intermediate has been proposed to explain the acylation.



KEYWORDS: acylation; pyrazolines; triazole; hybrids; hydrazones

INTRODUCTION

Amides and heterocyclic moieties are present in many bioactive natural products and commercial drugs exhibiting themselves as synthetic targets. Pyrazolines and their amide

derivatives *viz N*-acyl, *N*-sulfonamide and *N*-thiomide pyrazolines show interesting pharmacological profile such as anti-bacterial[1], anti-inflammatory and analgesic[2], anti-fungal[3], anti-tubercular[4], anti-cancer[5], anti-microbial[6] and anti-convulsant[7] activities, anti-inflammatory – antimicrobial agents[8] and MAO-inhibitors[9].

Bioactivities of various pyrazoline derivatives vide supra indicate that by varying the acyl side chain, a diversified bioactivity has been noted (Figure 1). Herein, it is pertinent to mention that a little emphasis has been focused on the synthesis of *N*-acyl pyrazoline with substituent in the acyl part. To the best of our knowledge, except *N*-acetyl-, *N*-propionyl- and *N*-α-chloroacetyl pyrazolines[10-16], no other substituted *N*-acyl pyrazolines have been reported.

The *N*-(substituted acyl) pyrazolines with varying substituents such as chloro- or hydroxy- or mercapto- group in the acyl moiety have been chosen for synthesis in the present investigation. The significance of choosing these substituents is to use them as potential synthons for the synthesis of hitherto unknown hybrid heterocyclic compounds *via* substitution and further modification.

On the other hand, venture into the synthesis of hybrid heterocycles as potential bioactive compounds is of recent interest. In this regard, we have reported[17] the synthesis and bioactivities of hybrid heterocycles *viz*. 1,2,3-triazolyl pyrazoline hybrids, 1,2,3-triazolyl-2-aminopyrimidine hybrids, 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids and 1,2,3-triazolyl indole hybrids.

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In view of the importance of *N*-acyl pyrazoline and hybrid heterocycles, we were prompted to synthesize acylated-pyrazolines and their triazole hybrids in the present research.

The acylation of alcohols, phenols and amines is an important transformation in organic synthesis. Acylation of such functional groups are often necessary during the course of various transformations in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products. Generally, acylation is carried out using acid chlorides or acid anhydrides with the usage of various catalysts such as $CoCl_2$,[18] Bu_3P,[19] Triflates,[20-24] $TaCl_5$,[25] zeolite,[26] clays,[27] ionic liquids,[28] $ZrOCl_2.8H_2O$,[29] alumina,[30] ZnO[31] and titanocene bis (perfluorooctanesulfonate).[32] However, in recent studies[33-38] acylating agents *viz*. acetyl chloride and acyl anhydride are used rarely due to their labile and hazardous nature. Moreover, some of the pyrazolines have been reported[39-41] as decomposable.

Interestingly and surprisingly, acylation of pyrazolines occurs with just carboxylic acid without any catalyst which seems to be noteworthy. Furthermore, so far no emphasis has been given for probing into the same and the acylating agent (formed if any) involved during the reaction. Hence, we were provoked to investigate on the same. This was because understanding (by tracing) the acylating intermediate involved, it would help to establish a new catalyst/activating agent-free acylating protocol with less hazardous and readily available carboxylic acids rather than the highly labile/reactive and hazardous

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conventional reagents and catalysts. In this regard, recently we have reported[17a] a probable mechanism for the same envisaging a transient acylating intermediate that might have been generated *insitu.* A deeper look on the same and its applicability has been focused and explored in the present study.

At the outset, a mixture of pyrazoline and acetic acid under refluxing temperature afford the *N*-acetyl pyrazoline in 95% yield in 1 h (Scheme 1). For further optimization, the reaction was carried out by varying the reaction temperature and time (Table 1, entries 1–5). The optimized temperature and time identified were 110 $^{\circ}$C and 1 hour in acetic acid wherein excellent yield of *N*-acetyl product (95 %) was noted. Interestingly, the acetylation is noted to proceed even at room temperature.

RESULTS AND DISCUSSION

Encouraged by the optimization, it was planned to explore the acylation of pyrazoline using various carboxylic acids as the acylating agent without any catalyst. The optimized condition was followed for the acylation of the pyrazoline with various carboxylic acids to synthesize the *N*-acylated pyrazolines (Table 2) and *N*-acylated pyrazoline-triazole hybrids (Table 3) in excellent yields.

Pyrazoline/pyrazoline-triazole hybrids were heated at 110 °C with liquid carboxylic acids such as acetic, propionic, butyric, thioglycolic and thiopropionic acids for an hour to afford corresponding *N*-acyl pyrazolines . Additionally, solid aliphatic acids such as phenyl-, phenoxy-, chloro- acetic acids and glycolic acid were used for acylation. In

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case of solid aliphatic acid the acylation was achieved in molten states. Further, the acylation was performed under aqueous condition, the results of which are presented in table 4. It is noteworthy that acetic acid/water ratio had an impact on the efficiency of acylation of pyrazoline. *i.e.* upto acetic acid/water ratio (50/50) (Table 4, entry 2 & 3), the yield of the product was good. Further by increasing the quantity of water in the ratio (Table 4, entry 4 & 5), no acylation occurred. Apparently, the poor solubility of pyrazoline in highly aqueous media would have hindered the reaction progress.

A plausible mechanism for *N*-acylation of pyrazolines (Scheme 2) using carboxylic acids is sketched below in which the product formation may be expected *via* three possible routes *viz*. route A, B & C. A transient acylating intermediate may be expected by the protonation of the imino nitrogen of the pyrazoline followed by the attack of the carboxylic acid at the imino carbon. In route A, an intermolecular attack of a lone pair on nitrogen atom on the carbonyl carbon of the intermediate may lead to the product III. On the other hand, route B deals with an intramolecular attack of a lone pair of the nitrogen atom on the carbonyl carbon of the intermediate may afford the same product. In route C, *insitu* formation of an anhydride may be expected to take place by the reaction of the intermediate with carboxylic acid, which may acylate the pyrazoline.

Having proposed the above possible routes for the acylation of pyrazolines with carboxylic acid, it was further attempted to investigate the most probable route. In this regard, external amine *viz.* benzyl amine was added into the reaction mixture (pyrazoline and acetic acid) and refluxed under the optimized reaction condition. The attempt

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resulted in the acylation of pyrazoline alone even though benzyl amine was present in the medium. This indicated that the reaction proceeds *via* the intramolecular pathway (route B) rather than the intermolecular mechanism. Had it been the intermolecular route, it should have afforded the *N*-acetyl pyrazoline and *N*-acetyl benzylamine. This was further confirmed unambiguously by treating a mixture of pyrazoline and benzylamine with acetic anhydride under refluxing condition identical to the above wherein *N*-acetylation of both occurred. Thus, the mechanism involved in the acylation of pyrazoline with carboxylic acid was unequivocally confirmed to be intramolecular.

It is pertinent to mention here that the above mechanism involving the initial protonation of the imino nitrogen of the hydrazone moiety of the pyrazoline followed by the attack of the carboxylic acid as nucleophile at the electrophilic imino carbon is supported by similar mechanism reported in the acylation of amines and alcohols using carbodimide[42].

Having investigated the mechanism and its applicability, we were interested to investigate the acylation of partial skeletons of pyrazolines to develop further insight into the mechanism so that its applicability can be expanded and generalized towards a common acylation reaction using carboxylic acid.

In this regard, the partial skeletons (**A & B**) (figure 2) of pyrazoline were refluxed with acetic acid and the product identified. With regard to the partial skeleton, hydrazones of benzaldehyde and acetophenone were individually treated with acetic acid under optimized condition. It was notable that at the outset the reaction was not smooth

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affording a viscous unidentifiable product. Literature data related to this was noted in a patent[43.] wherein hydrazones get acylated with a slight modified reaction condition *viz.* one pot synthesis of acylation of hydrazone. However, the work was restricted only to acylation with acetic acid. So we planned to apply this protocol to generalize the same and hence landed successfully in the acylation of hydrazones with different carboxylic acids in very excellent yields (Table 5).

In conclusion, the present study discloses that the *N*-acylation of pyrazoline readily occurs using carboxylic acids as the acylating agent without any catalyst /activating agent. The investigation proposes an interesting mechanism *via* the *insitu* generation of transient acylating intermediate as an acyl group contributor. The novel synthetic protocol has been applied for the synthesis of a variety of *N*-acyl pyrazolines and their triazole hybrids. Further studies in this regard is under progress which may pave way for the development of a general novel new acylating protocol in organic synthesis using carboxylic acids without catalyst/activating agents.

EXPERIMENTAL

General

All chemicals, reagents, and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd. India. Silica gel (60–120 mesh) was used for column chromatographic isolation and purification of the compounds synthesized. Melting points were obtained on electro-thermal apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance

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(300 MHz) spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with coupling constant (J) values in Hertz

General Procedure for The Synthesis of Pyrazolines[44]

Equimolar quantities of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (1 mmol) and hydrazine hydrate (1 mmol) in ethanol (10 mL) was refluxed for 3 hours. The resulting mixture was poured onto crushed ice. The solid obtained was filtered as the pure product.

General Procedure for Acylation of 5-(4-Methoxyphenyl)-3-Phenyl-4,5-Dihydro-1*H*-Pyrazole

5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole **1** (1 mmol), was dissolved in carboxylic acids (2 mL) **2** and heated at 110 °C for an hour. After the completion of the reaction (monitored by TLC), the mixture was treated with aqueous sodium bicarbonate to neutralize the excess acid. Then the reaction mixture was extracted with dichloromethane to separate the organic layer and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using pet ether: ethyl acetate (93:7) as the eluent to afford the pure products (**3a**-**3i**) in excellent yields (91-95 %). While compounds **3a**[10], **3b**[11], **3f**[12]are known, others are hitherto unknown compounds.

1-(5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)butan-1-one (**3c**). Yield: 94%. White solid. M.p. 105-107 °C. FTIR (KBr) υ /cm^{-1} 1658, 1599. ^{1}H NMR (300

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MHz, $CDCl_3$): δ 7.74 (d, *J* = 6.7 Hz, 2H); 7.47 – 7.37 (m, 3H); 7.15 (d, *J* = 8.7 Hz, 2H); 6.82 (d, *J* = 8.7 Hz, 2H); 5.52 (dd, *J* = 11.8, 4.6 Hz, 1H); 3.74 (s, 3H); 3.71 – 3.61 (m, 1H); 3.11 (dd, *J* = 17.7, 4.6 Hz, 1H); 2.77 (ddd, *J* = 15.0, 9.0 Hz, 2H); 1.79 – 1.66 (m, 2H); 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0; 158.6; 153.1; 134.0; 131.3; 129.9; 128.4; 126.6; 126.2; 125.1; 113.9; 59.2; 54.8; 41.7; 35.8; 18.1; 13.7. Anal. Calcld. for (%) $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; Found : C 74.57, H 6.93, N, 8.74.

General Procedure for the Synthesis of Triazole-Pyrazoline Hybrids

Equimolar quantities of 1-(1-Benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-(4-methoxyphenyl) but-3-en-1-one (1 mmol) and hydrazine hydrate (1 mmol) in Ethanol (10 mL) was refluxed for 3 hours. The resulting mixture was poured onto crushed ice. The solid obtained was filtered as a pure product.

General Procedure for the Acylation of 1-Benzyl-4-(5-(4-Methoxybenzyl)-4,5-Dihydro-1*H*-Pyrazol-3-Yl)-5-Methyl-1*H*-1,2,3-Triazole

1-Benzyl-4-(5-(4-methoxybenzyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-5-methyl-1*H*-1,2,3-triazole **1** (1 mmol) in carboxylic acids (2 mL) **2** was heated at 110 °C for 1 hour. After the completion of the reaction (as monitored by TLC), the mixture was treated with aqueous sodium bicarbonate to wash the excess acid. Then the reaction mixture was extracted with dichloromethane to separate the organic layer and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using pet ether: ethyl acetate (90:10) as the eluent to afford the

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pure products (**3j-r**) in excellent yields (89-94 %). While compounds (**3j**& **3k**)[17] are known, other compounds are hitherto unknown.

1-(3-(1-Benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)butan-1-one (**3l**). Yield: 94%. Gummy matter. FTIR (KBr) υ /cm^{-1} 1626, 1568. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 3H); 7.23 – 7.11 (m, 2H); 6.94 (d, *J* = 7.4 Hz, 2H); 6.83 (d, *J* = 8.0 Hz, 2H); 5.55 (s, 2H); 5.49 (dd, *J* = 12.0, 4.4 Hz, 1H); 3.83 – 3.72 (m,1H); 3.77 (s, 3H); 3.43 (dd, *J* = 18.3, 4.4 Hz, 1H); 2.65 (dd, *J* = 14.0, 7.0 Hz, 2H); 2.52 (s, 3H); 1.83 – 1.54 (m, 2H); 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8; 158.5; 149.0; 137.8; 133.9; 133.6; 132.7; 128.7; 128.1; 126.9; 126.6; 113.8; 58.0; 54.8; 51.5; 42.7; 35.8; 18.0; 13.7; 9.1. Anal. Calcld. for (%) $C_{24}H_{27}N_5O_2$: C 69.04, H 6.52, N 16.77; Found: C 69.08, H 6.50, N 16.81.

General Procedure for the Synthesis of *N*-Acyl Hyrazones (8a-I)

Acetophenone/benzaldehyde or 1-(1-Benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone **5** (1 mmol), was dissolved in carboxylic acids (2 mL) **2** to which hydrazine hydrate **6** (1 mmol), was added slowly while the mixture was maintained in ice cold condition with stirring for 30 min. Then the mixture was allowed to reach the room temperature and then heated to reflux for 6 hours. Then it was treated with aqueous $NaHCO_3$ solution followed by the extraction with dichloromethane. Then, the organic layer was separated and dried over anhydrous Na_2SO_4. It was then separated by column chromatography using petroleum ether: ethyl acetate (93:7) as the eluent to afford the product (**8a-i**) in excellent yields (90-94 %). While compound **8a**[43]is known, others are hitherto unknown.

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N'-(1-Phenylethylidene)propionohydrazide (**8b**). Yield: 93%. White solid. M.p. 137-139 °C. FTIR (KBr) υ /cm^{-1} 1676, 1560. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H); 8.00 – 7.61 (m, 2H); 7.71 – 7.41 (m, 3H); 2.82 (q, *J* = 7.5 Hz, 2H); 2.22 (s, 3H); 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6; 147.1; 138.1; 128.7; 128.1; 125.8; 26.0; 12.8; 8.6. Anal. Calcld. for (%) $C_{11}H_{14}N_2O$: C 69.45; H 7.42, N 14.73; Found: C 69.48, H 7.47, N 14.70.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website

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Table 1. Optimization of temperature/time in the synthesis of *N*-AcetylPyrazolines **3a**

Entry	Temp [°C]	Time [h]	Yield [%][a]
1	RT	8	45
2	70-80	1	60
3	70-80	2	70
4	70-80	3	85
5	110	1	95

[a]Isolated yield

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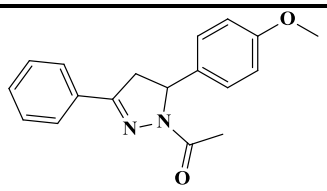
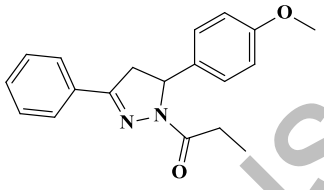
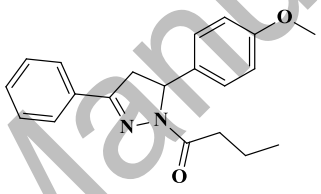
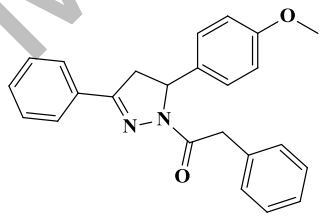
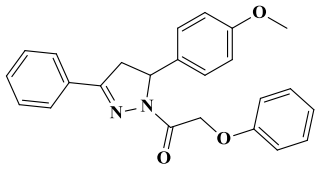
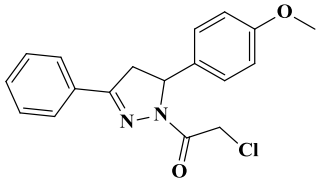
Table 2. Synthesis of *N*-acylated pyrazolines **3a-i**

Entry	Substrate **1**	Acids	Product	Yield [%][a]
1	1	acetic acid	 **3a**	95
2	1	propionic acid	 **3b**	92
3	1	butyric acid	 **3c**	94
4	1	phenyl acetic acid	 **3d**	91
5	1	phenoxy acetic acid	 **3e**	93
6	1	chloro acetic acid	 **3f**	94

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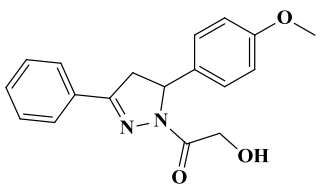
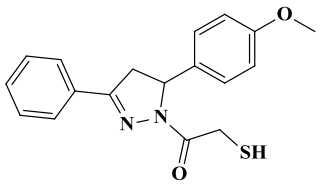
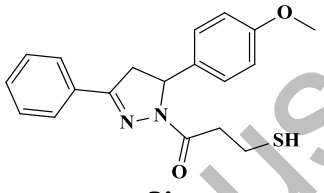
7	1	glycolic acid	 **3g**	91
8	1	thioglycolic acid	 **3h**	90
9	1	thiopropionic acid	 **3i**	92

[a]Isolated yield

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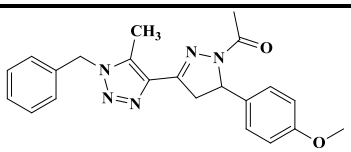
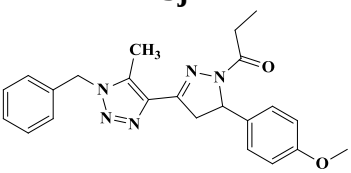
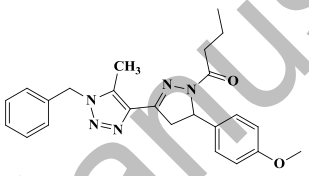
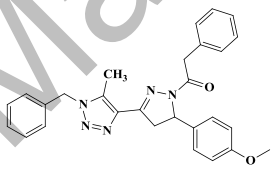
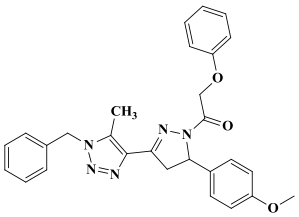
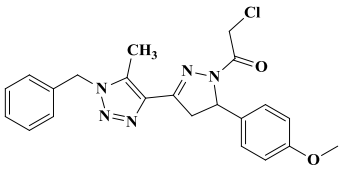
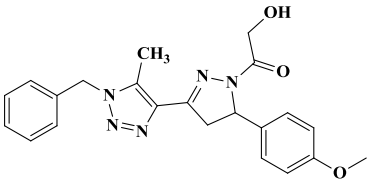
Table 3. Synthesis of *N*-acylated pyrazoline-triazole hybrids **3j-r**

Entry	Substrate **1a**	Acids	Product	Yield [%][a]
1	1a	acetic acid	 **3j**	92
2	1a	propionic acid	 **3k**	90
3	1a	butyric acid	 **3l**	94
4	1a	phenyl acetic acid	 **3m**	91
5	1a	phenoxy acetic acid	 **3n**	89
6	1a	chloro acetic acid	 **3o**	91
7	1a	glycolic acid	 **3p**	93

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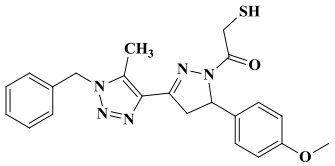
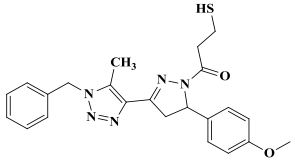
8	1a	thioglycolic acid	 **3q**	92
9	1a	thiopropionic acid	 **3r**	94

[a]Isolated yield

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Table 4. Screening of AcOH / Water ratio in the synthesis of *N*-acetyl pyrazoline **3a**

Entry	AcOH /Water Ratio	Yield[%][a]
1	100/0	95
2	70/30	89
3	50/50	83
4	30/70	No reaction
5	10/90	No reaction

[a]Isolated yield

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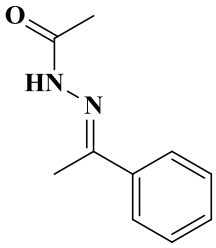
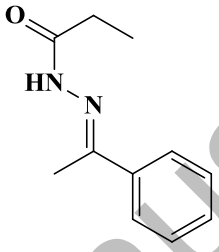
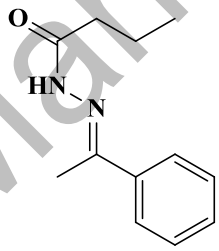
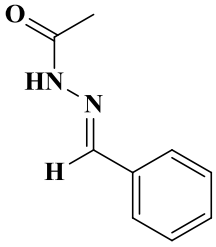
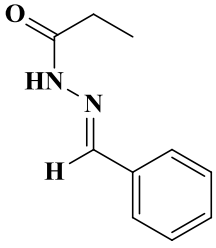
Table 5. Synthesis of *N*-acylated hydrazones **8a-i**

Entry	Substrate	Acids	Product	Yield [%][a]
1	**5**	acetic acid	 **8a**	91
2	**5**	propionic acid	 **8b**	93
3	**5**	butyric acid	 **8c**	92
4	**5a**	acetic acid	 **8d**	93
5	**5a**	propionic acid	 **8e**	90

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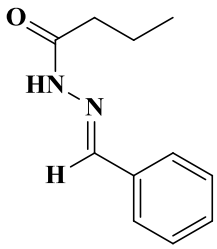
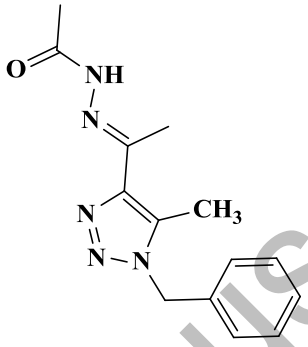
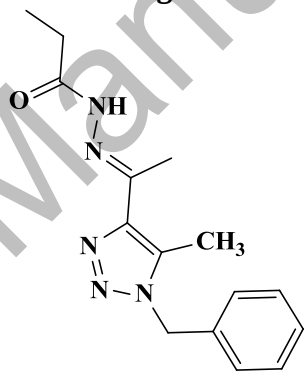
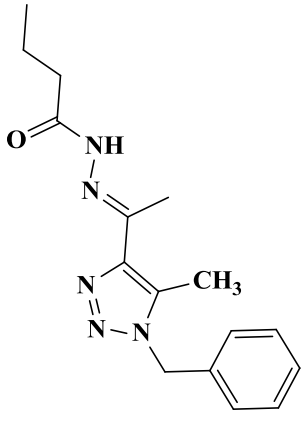
6	**5a**	butyric acid	 **8f**	94
7	**5b**	acetic acid	 **8g**	93
8	**5b**	propionic acid	 **8h**	91
9	**5b**	butyric acid	 **8i**	90

[a]Isolated yield.

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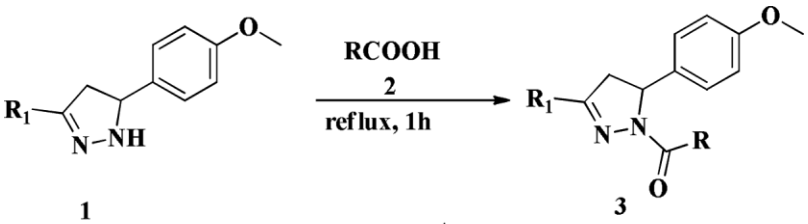
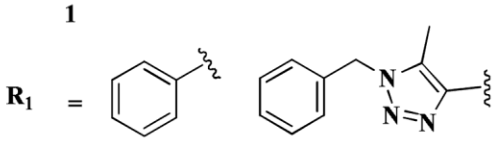
Scheme 1. Synthesis of *N*-acylated pyrazolines/ *N*-acylated pyrazoline-triazole hybrids



1 3



R= -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$C_6H_5CH_2$, -$C_6H_5OCH_2$, -CH_2 SH, -CH_2CH_2 SH, -CH_2 Cl, -CH_2 OH

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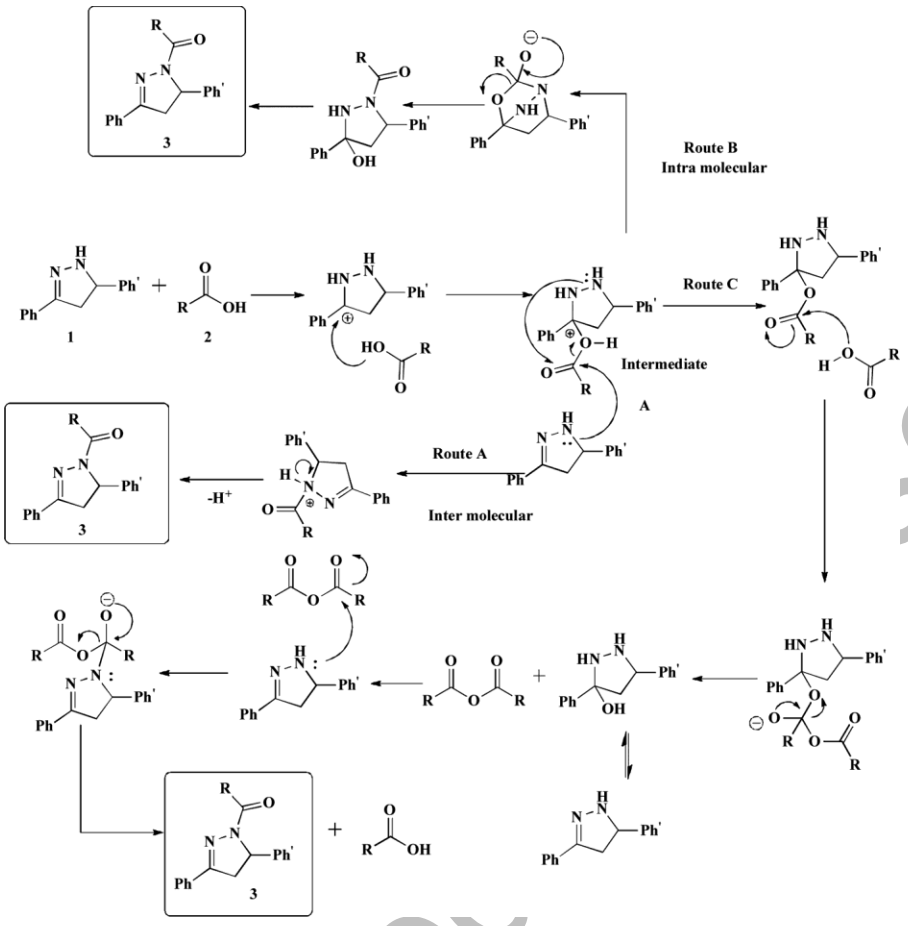
Scheme 2. Plausible mechanism for *N*-acylation



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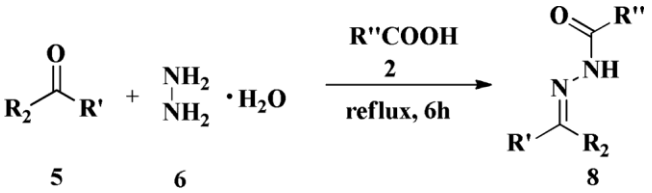
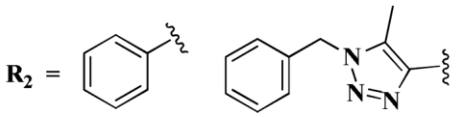
Scheme 3. Synthesis of *N*-acyl hydrazones



R'= H; CH_3



R''= -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$,

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Figure 1. Some biologically potent pyrazolines and *N*-acyl pyrazolines

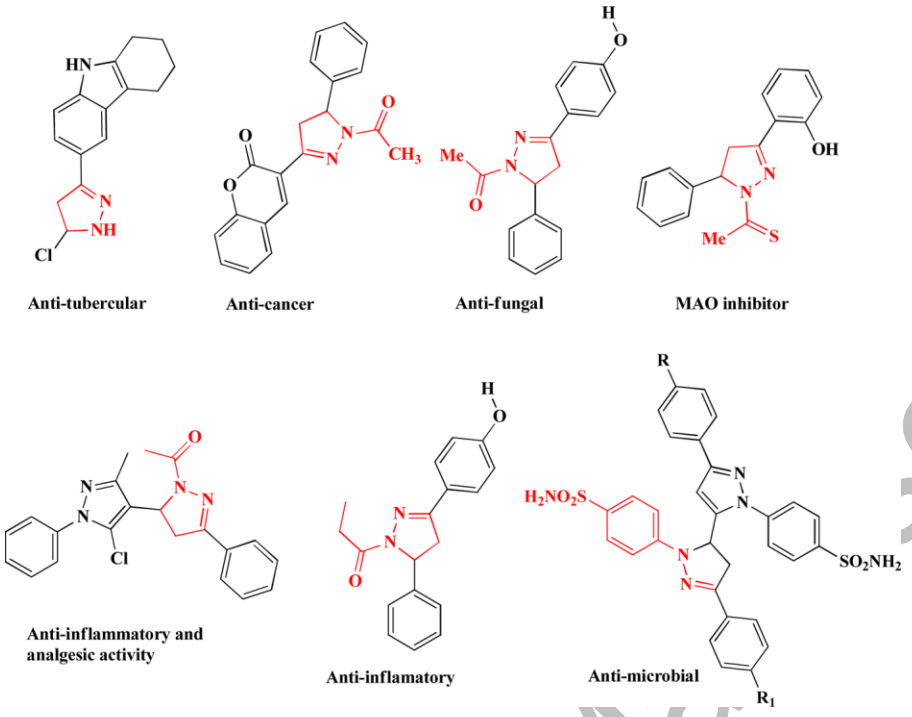

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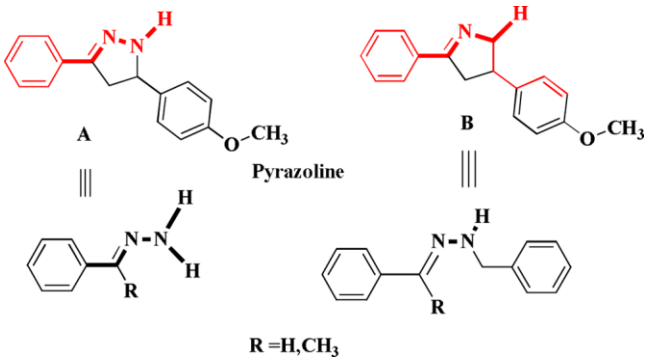
Figure 2. Partial skeletons of pyrazoline.



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