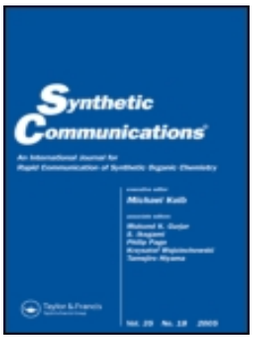

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Novel, Simple, and Efficient Synthesis of 3-(2-(5-(Benzylideneamino)-3-phenyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one Derivatives via a One-Pot, Four-Component Condensation Reaction

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NOVEL, SIMPLE, AND EFFICIENT SYNTHESIS OF 3-(2-(5-(BENZYLIDENEAMINO)-3-PHENYL-1*H*-PYRAZOL-1-YL)THIAZOL-4-YL)-4-HYDROXY-6-METHYL-2*H*-PYRAN-2-ONE DERIVATIVES VIA A ONE-POT, FOUR-COMPONENT CONDENSATION REACTION

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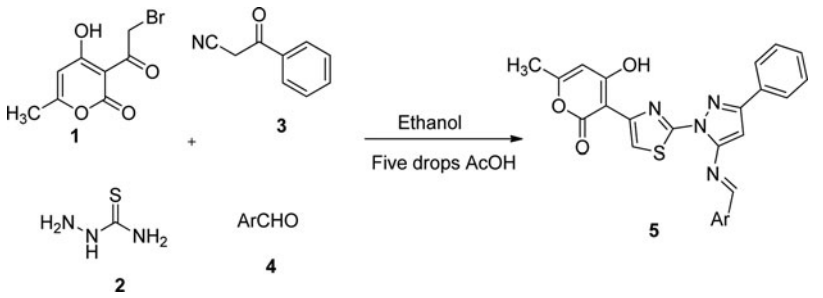
GRAPHICAL ABSTRACT



Abstract *The synthesis of 3-(2-(5-(benzylideneamino)-3-phenyl-1H-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one derivatives was achieved through a one-pot, four-component reaction involving condensation of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one, thiosemicarbazide, phenacylcyanaide, and various aryl aldehydes in dry alcohol and few drops of acetic acid under reflux condition. This four-component reaction has some advantages such as ease of handling, good yields, and easy workup. All structures of newly prepared compounds were confirmed by analytical and spectral data.*

Keywords Aryl aldehyde; 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2 h-pyran-2-one; one-pot four-component condensation reaction; phenacylcyanaide; pyrazolo-thiazolyl derivatives; thiosemicarbazide

INTRODUCTION

Pyrazole and thiazole derivatives are used in medicine because of their large number of pharmacological activities.[1] Pyrazole and its derivatives constitute an important class of compounds and attract widespread attention because of pharmacological properties such as analgesic and anti-inflammatory properties.[2,3] The

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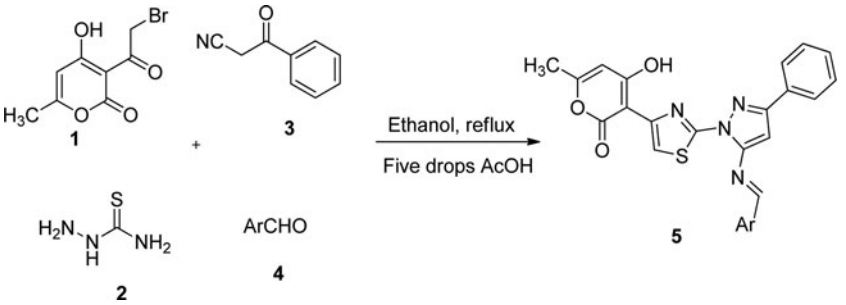
pyrazole moiety has an important role in some drug structures; for example, some arylpyrazole derivatives have anti-HIV-1 activity.[4–6] Thiazoles are an important class of natural and synthetic compounds. Thiazoles and their derivatives have been reported to possess antibacterial,[7] antifungal,[8] antioxidant,[9] anti-HIV,[10] and antiallergic[11] activities.

Recently, multicomponent reactions (MCRs)[12] have played a significant role in modern synthetic organic chemistry wherein three or more reactants are added together in one pot to result in diverse bioactive heterocyclic compounds. Multicomponent reactions have emerged as an important tool for building diverse and complex organic molecules through carbon–carbon and carbon–heteroatom bond formation, which takes place in a tandem manner.[13] We designed the synthesis of novel substituted pyrazolo thiazolyl derivatives starting from bromodehydroacetic acid, phenacylcyanaide, thiosemicarbazide, and various araldehydes.

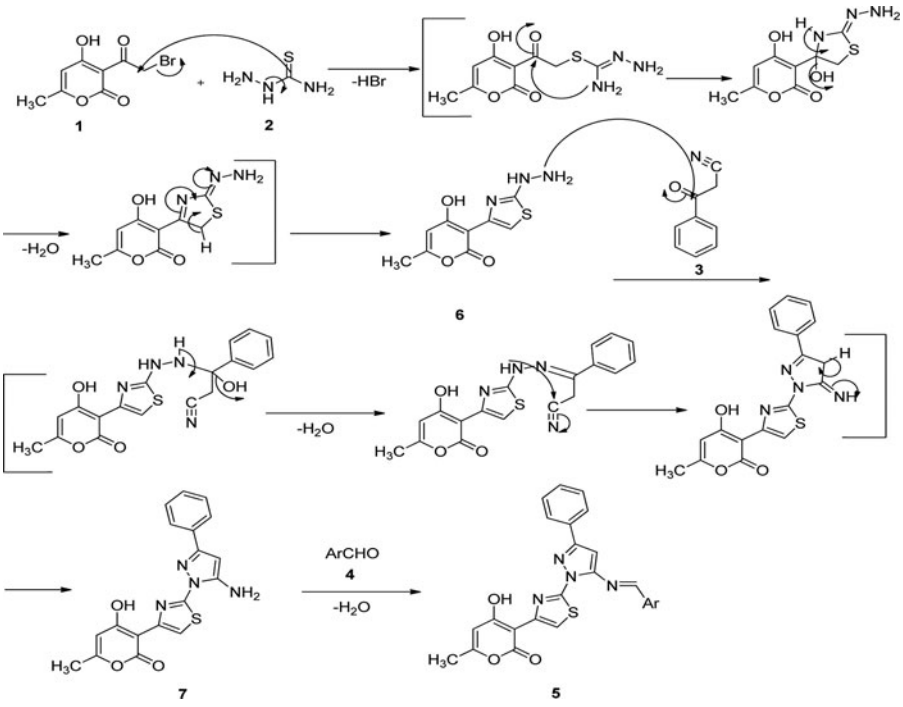
RESULTS AND DISCUSSION

This is a one-pot, four-component synthesis of substituted pyrazolo thiazole derivatives. Refluxing an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiosemicarbazide and phenacylcyanaide in absolute ethanol and few drops of glacial acetic acid for 4 h resulted in the formation of amino derivatives. These undergo condensation with various benzaldehydes to give the final products 3-(2-(5-(benzylideneamino)-3-phenyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one derivatives **5** (Scheme 1). The importance of this reaction is that two rings like thiazole and pyrazole are formed simultaneously, wherein the first step is Hantzsch thiazole synthesis and the next step is formation of a pyrazole ring at the second position of the thiazole ring. This is a novel observation and new heterocyclization reactions form many bonds at a time.

A plausible mechanism for the formation of title compound **5** is shown in Scheme 2. The initial step is the formation of 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **6** from the reaction between 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and thiosemicarbazide **2.** Intermediate **6** is on reaction with phenacylcyanaide **3** to form another intermediate 3-(2-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **7,** and then its reacts



Scheme 1. Preparation of pyrazolo-thiazolyl derivatives.



Scheme 2. Reaction mechanism for the formation of final compounds **5**.

with various benzaldehydes to give corresponding title compound **5** as shown in Scheme 2.

In the IR spectrum of **5a,** the OH appeared at 3422 cm^{-1}, lactone carbonyl at 1721 cm^{-1}, and C=N at 1607 cm^{-1}, respectively. The ^{1}H NMR spectrum of **5a** showed five singlets at $\delta = 2.23$, 6.17, 6.89, 8.26, and 12.32 ppm, which were due to methyl, pyran, pyrazole, -ArCH=N, hydroxy protons, and multiplets at $\delta = 7.24$–7.71 ppm for nine aromatic protons and one thiazole proton respectively. In the mass spectrum **5a** showed at $[M + H]^+$ ion at m/z 489.

CONCLUSION

In conclusion, we have described a new method for the synthesis of 3-(2-(5-(benzylideneamino)-3-phenyl-1*H*-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-ones. The reaction proceeds via a one-pot, four-component reaction. The advantages of this synthetic protocol are mild reaction conditions, shorter reaction times, easy workup, and excellent yields.

EXPERIMENTAL

All the reagents, solvents, and 3-oxo-3-phenylpropanenitrile were purchased from commercial sources and were used without any further purification unless otherwise stated. 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one[14] was prepared

Table 1. Synthesis of title compound **5** data

Entry	ArCHO	Product	Time (h)	Yield (%)
1	4-Chlorobenzaldehyde	**5a**	8	85
2	4-Methoxybenzaldehyde	**5b**	8	86
3	4-Bromobenzaldehyde	**5c**	7	88
4	3,4-Dimethoxybenzaldehyde	**5d**	8	82
5	4-(Dimethylamino)benzaldehyde	**5e**	8	80
6	4-Hydroxybenzaldehyde	**5f**	8	80
7	3-Nitrobenzaldehyde	**5 g**	7	81
8	4-Hydroxy-3-methoxybenzaldehyde	**5 h**	8	80
9	Naphthaldehyde	**5i**	7	79
10	2-Hydroxy-3-methoxybenzaldehyde	**5j**	8	82
11	2-Hydroxybenzaldehyde	**5k**	8	83
12	2,3,4-Trimethoxybenzaldehyde	**5 l**	7	86

according to the literature procedure. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatography (TLC) plates (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as standard. Mass spectra (EI-MS) were determined on a Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

A mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (1 mmol), thiosemicarbazide **2** (1 mmol) and phenacyl cyanide **3** (1 mmol) was taken in 10 ml of ethanol and five drops of glacial acetic acid. The reaction mixture was refluxed at 60 °C for about 4 h, and 4-chlorobenzaldehyde **4** (1 mmol) was added. The reaction mixture was refluxed for 4 h and then cooled to room temperature. The solid obtained was filtered, washed with water, and recrystallized from methanol to give excellent yields of products (Table 1). Yellow solid, mp 181–183 °C; IR (KBr) (υ_{max}/cm^{-1}): 3432, 1721, 1607; ^{1}H NMR (400 MHz, DMSO-d_6) 2.23 (s, 3H, CH_3), 6.17 (s, 1H, pyran proton), 6.89 (s, 1H, pyrazole proton), 7.24–7.71 (m, 10H, 1H thiazole & 9H ArH), 8.26 (s, 1H, -CH=Ar), 12.32 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) 22.1, 98.2, 100.0, 108.2, 123.5, 127.6, 128.0, 129.7, 130.0, 131.2, 132.3, 134.0, 135.5, 145.2, 148.3, 152.1, 157.2, 159.8, 162.7, 165.6, 194.0; mass spectrum m/z: 489 ($M^+ + 1$). Anal. calcd. for $C_{25}H_{17}ClN_4O_3S$: C, 61.41; H, 3.50; N, 11.46%. Found: C, 61.46; H, 3.43; N, 11.54%.

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SUPPLEMENTAL MATERIAL

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

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