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Regioselective synthesis of novel substituted pyrazolo[1,5-*a*]pyrimidines under solvent-free conditions

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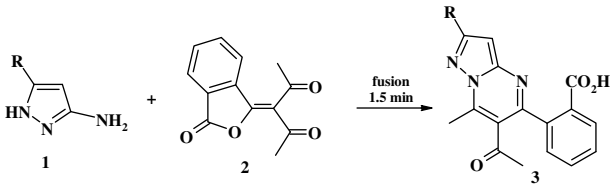
ABSTRACT

A series of 6-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidines **5** have been synthesized directly by the solvent-free reaction between 5-amino-1*H*-pyrazoles **1** and 3-benzoyl-2-methyl-4*H*-chromen-4-one **4**. This solvent-free reaction proceeds in a regiospecific fashion by intramolecular opening of the γ-pyrone ring in a Michael-type reaction, that followed by cyclization via nucleophilic attack of endocyclic pyrazole nitrogen toward benzoyl group gives the pyrazolo[1,5-*a*]pyrimidines **5**. The use of this method affords high yields in short reaction times.

Pyrazole and pyrimidine derivatives have attracted the attention of organic chemists very much due to their biological and chemotherapeutic importance. Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit a wide range of biological activities, such as **cSRC** kinase inhibitors involved with ischemic brain pathology,[1] cyclin dependent kinase 1 (**CDK1**) inhibitor,[2] **HIV** reverse transcriptase inhibitors,[3] **CCR1** antagonists,[4] protein kinase inhibitors,[5] **cGMP** degradation inhibitors, or herbicidal and fungicidal activities.[6] These compounds can also be used as intermediates in the dyestuff industry.[7] Numerous methods for the synthesis of pyrazolo[1,5-*a*]pyrimidines have been reported in the last twenty years, which involved the reaction between 5-aminopyrazoles and 1,3-bis-electrophilic compounds, such as β-dicarbonyl, alkoxymethylene-β-dicarbonyl, and β-enaminone compounds.[8,9]

We have already reported studies on reactions involving some alkoxymethylene-β-dicarbonyl compounds, that if containing a cyclic structure may allow the introduction of polyfunctionality in the pyrazolo[1,5-*a*]pyrimidine system, such as the phenolic[9a] or benzoic acid[9b] residues. Recently, we have described the synthesis of new 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)benzoic acids **3** by the solvent-free cyclocondensation between 5-amino-1*H*-pyrazoles **1** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)-pentane-2,4-dione **2** in good to excellent yields and short reaction times (Scheme 1).[9b]



R = CH_3, *t*-Bu, C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 1.

Accordingly, the 1,3-biselectrophilic analogous like chromones (see **4** in Scheme 2) represent a very reactive system owing to the presence of an unsaturated β-diketone moiety, which makes the position C2 sensitive to Michael addition of nucleophiles with opening of the γ-pyrone ring and followed by a new cyclocondensation via one of those carbonyl groups.[9,10]

Continuing our studies on the application of solvent-free cyclocondensation methodology to the synthesis of fused pyrazoles,[11] we described here the solvent-free reaction between 5-amino-1*H*-pyrazoles **1** and 3-benzoyl-2-methyl-4*H*-chromen-4-one **4**, which afforded successfully an interesting series of 6-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidines **5a–h** after just a few minutes[12] (Scheme 2). The synthesis has been carried out using two different methods. In the first (method A), the reaction mixture was placed in an air open Pyrex-tube and the system was heated in an oil-bath at 180 °C for 2.0 min to give **5**

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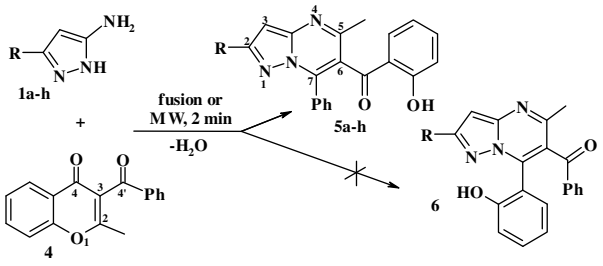


Entry	R	Yield., %*
5a	CH_3	75/93
5b	*t*-Bu	73/92
5c	C_6H_5	72/90
5d	4-$CH_3C_6H_4$	70/91
5e	4-$CH_3OC_6H_4$	72/89
5f	4-$O_2NC_6H_4$	75/88
5g	4-ClC_6H_4	76/91
5h	4-BrC_6H_4	70/91

* Yield by fusion/MW

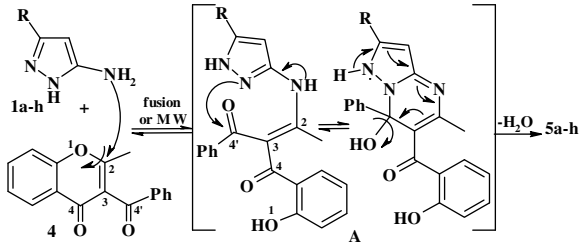
Scheme 2.

in good isolated yield (70–76%). In the second (Method B), the reaction mixture was placed in an air open Pyrex-erlenmeyer flask and the system was irradiated in a multimode microwave oven during 2 min (at 600 W) to give **5** in excellent yield (88–93%). The reactions were repeated in different domestic microwave ovens to prove reproducibility, and no significant deviation was found.

It is worthy of mentioning that the goodness and simplicity of this process is due to the fact that these new compounds are isolated in good yields as stable crystalline solids and easily purified by recrystallization from ethanol. These reactions proceed in a regioselective fashion, with no evidence of formation of the regioisomer derivatives **6**; and the use of the 3-benzoyl-2-methyl-4*H*-chromen-4-one **4** allows the introduction of polyfunctionality in the pyrazolo[1,5-*a*]pyrimidines, such as the 2-hydroxybenzoyl group.

Taking into account the reports of the literature,[9,10] we have postulated a route for the formation of pyrazolo[1,5-*a*]pyrimidines **5a–h**. As initial stage, we assume a Michael-type nucleophilic addition of NH_2-group of amine **1** towards the **C2** of compound **4**, as explained above. The addition is followed with ring-opening of the γ-pyrone to give the intermediate **A**, which can then evolve by cyclocondensation via attack of the nucleophilic nitrogen at the pyrazole toward the carbonyl group of the benzoyl group to form the isolated compounds **5** (Scheme 3).

It is quite evident that the last step of cyclocondensation occurs with the participation of the carbonyl at benzoyl group (**C4′**) instead of carbonyl group at 2-hydroxybenzoyl (**C4**). The reason is the electron releasing effect of the phenolic group which precludes this carbonyl for the nucleophilic addition, favoring so the regioselectivity in the reaction.



Scheme 3.

The structures of new pyrazolo[1,5-*a*]pyrimidines were appropriately established by the usual spectroscopic methods. Single crystal X-ray diffraction analysis of some selected compounds was used to corroborate the postulated structures.[13]

Concluding, we have developed a simple, efficient, and versatile one-step method for the synthesis of functionalized pyrazolo-[1,5-*a*]pyrimidines **5a–h** in a regiochemical manner by reaction between aminopyrazole **1** with the chromenone **4**. These compounds present a privileged core from a biological point of view. The reaction induced by microwave offered better yields than the reaction carried out by heating in an oil-bath.

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12. *Preparation of 6-(2′-hydroxybenzoyl)-5-methyl-7-phenyl-pyrazolo[1,5-a]-pyrimidines* **5a–h**: A mixture of equimolar amounts of 5-*amino-3-R-1H-pyrazole* **1** (10 mmol) and *3-benzoyl-2-methyl-4H-chromen-4-one* **4** (2.64 g, 10 mmol) was heated in an oil-bath at 180 °C for 2 min (Method A) or was placed in an air open Pyrex-erlenmeyer flask, and the system was irradiated in a multimode microwave oven during 2 min (at 600 W) (Method B). It was then stirred and allowed to cool to room temperature till it solidified. The solid material was treated with ethanol. After the solvent was removed by filtration, the products formed were recrystallized from ethanol. *Data for 6-(2′-hydroxybenzoyl)-5-methyl-2-(4-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine* **5d**: This compound was obtained according to general procedure as yellow crystals. Mp 198–199 °C, yield 70/91%. IR (KBr) = 3423 cm^{-1} (OH), 1698 cm^{-1} (C=O), 1595 cm^{-1} (C=N); ^1H NMR (DMSO-d_6, 400 MHz) δ: 2.33 (s, 3H, *p*-CH_3),

2.42 (s, 3H, 5-CH_3), 6.76 (t, 1H, H-5*Bz*, *J* = 7.45 and 7.44 Hz), 6.83 (d, 1H, H-3*Bz*, *J* = 8.28 Hz), 7.21 (s, 1H, H-3), 7.25 (d, 2H, H*m*R, *J* = 7.86 Hz), 7.40 (m, 4H, H*m*Ph, H-4*Bz* and H-6*Bz*), 7.54 (m, 3H, H*p*Ph and H*o*Ph), 7.81 (d, 2H, H*o*R, *J* = 7.85 Hz), 10.95 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 20.9 *p*-CH_3, 23.2 5-CH_3, 92.7 C3, 117.4 C3*Bz*, 119.4 C5*Bz*, 121.4 C6, 122.4 C1*Bz*, 126.1 C*o*R, 128.1 C*m*Ph, 129.2 C*i*Ph, 129.3 C*m*R, 129.6 C*i*R, 129.7 C*o*Ph, 130.4 C4*Bz*, 131.8 C*p*Ph, 136.5 C6*Bz*, 138.6 C*p*R, 142.6 C7, 148.9 C3a, 155.1 C5, 155.7 C2, 159.8 C2*Bz*, 193.6 C=O; MS (70 eV) *m*/*z* (%): 419 (89, M^+), 404 (19), 298 (42), 299 (100), 77 (19), 39 (29). HRMS: calcd for $C_{27}H_{21}N_3O_2$: *m*/*z* = 419.1634; found: 419.1639.

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