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

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Abstract—A series of 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)benzoic acids **5** has been prepared by a novel protocol that uses the fusion method between 5-amino-1*H*-pyrazoles **4** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione **3**. The use of this novel protocol renders good to excellent yields along with short reaction times. In addition, this solvent-free cyclocondensation proceeds in a regiospecific fashion by intramolecular ring opening of the furane ring in a Michael-type reaction.

1. Introduction

Pyrazolo[1,5-*a*]pyrimidines are purine analogues with useful properties as antimetabolites in purine biochemical reactions, that have displayed wide pharmacological applications due to their antitrypanosomal[1] and antischistosomal[2] activities, their sedative and anxiolitic-like properties[3] and their potential as HMG-CoA reductase inhibitors,[4] COX-2-selective inhibitors,[5] AMP phosphodiesterase inhibitors,[6] KDR kinase inhibitors[7] and selective peripheral benzodiazepine receptor ligands.[8] These interesting biological properties have prompted the development of new procedures for the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives.[9] Various methods of synthesis that have been described in the past involved the reaction between 5-aminopyrazoles with 1,3-bielectrophilic compounds, such as β-dicarbonyl, alkoxymethylene-β-dicarbonyl and β-enaminone compounds.[10]

On the other hand, benzoic acid or benzoate salts, which remain widely used as food preservatives,[11] have exhibited some biological properties and drug–drug interactions.[12] The benzoic residue is also present in a variety of pharmacologically active compounds. For example, 5-aminosalicylic acid has shown inhibition of thiopurine methyltransferase, as well as drug–drug interaction with sulfasalazinem[13] and has been used as a anti-lipidemidic agent[14] or as a modulator in drug pharmacokinetics.[15]

Here, we report a new synthetic procedure that incorporates both systems, that is, pyrazolo[1,5-*a*]pyrimidine and benzoic residues, into a single molecule. Compared to those compounds having either functionality, the new molecule is expected to exhibit enhanced biological activity. In this way, while using a friendly environmental protocol,[16] we have adapted the known method using β-enaminones and aminopyrazol to the preparation of pyrazolo[1,5-*a*]pyrimidines, but including this time a cyclic bivalent leaving group that would result in a benzoic residue after condensation. We hypothesize that the condensation adduct of phthalic anhydride and a 1,3-dicarbonyl derivative could fulfil such expectation, and hence 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione was prepared as described recently (see Scheme 1).[17]

2. Results and discussion

Continuing our studies on the application of solvent-free cyclocondensation procedures in the synthesis of fused pyrazoles,[16] our early efforts involved the use of a fusion method between 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)-pentane-2,4-dione **3** and aminopyrazoles **4** in equimolecular amounts by heating in an oil-bath at 150 °C, that

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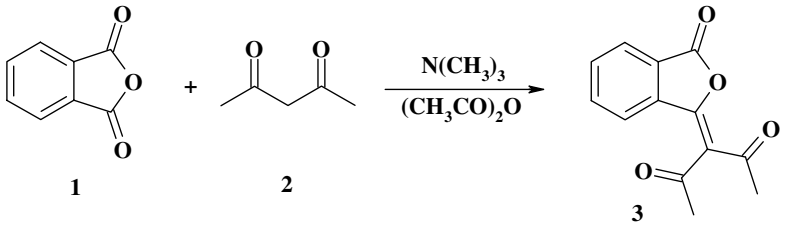
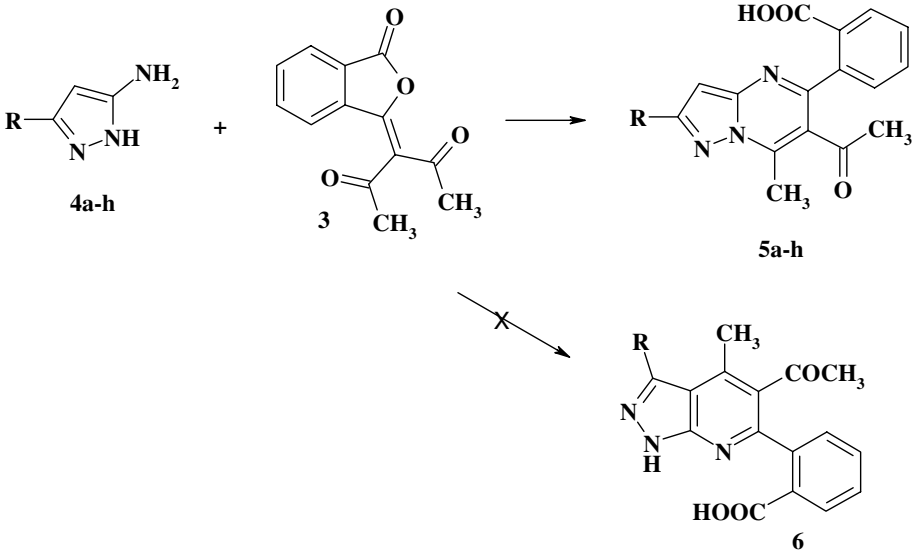


Scheme 1.

afforded successfully the desired 2-(6-acetyl-2-R-7-methylpyrazolo[1,5-*a*]pyrimidin-5-yl)benzoic acids **5a**–**h** after just a few minutes[18] (Scheme 2). It is worth mentioning that the goodness and simplicity of this process is due to the fact that the new compounds were obtained in excellent yields as stable crystalline solids and easily purified by recrystallization from ethanol. In addition, compounds **5** were prepared in a regioselective fashion with participation of the new reagent **3**, which allows the introduction of polyfunctionality in the pyrazolo[1,5-*a*]pyrimidines, such as the benzoic acid residue. No evidence of the regioisomer derivative **6** was found.

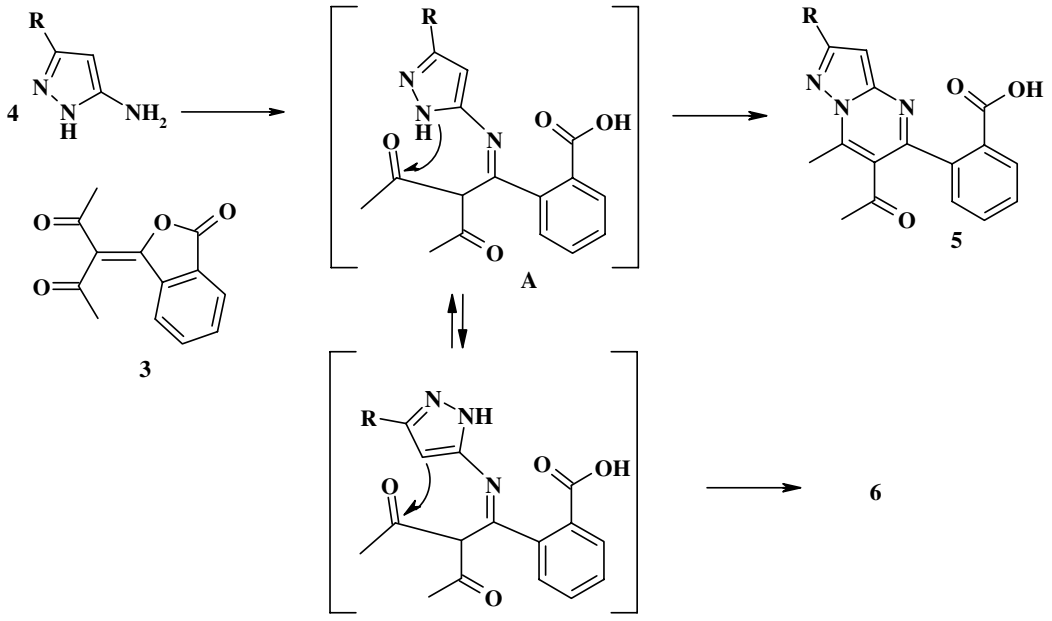
The structure of compound **5a**–**h** was appropriately established by spectroscopic and analytical methods. NMR data were consistent with structures **5** and, for example, the ^{1}H NMR spectrum for compound **5a** exhibits a sharp singlet at 6.57 and another wide singlet at 13.01 ppm, corresponding to the =CH–pyrazolic proton at positions 3 and to the CO_2H-group, respectively. The presence of these signals agrees with the proposed structure reaction route, discarding the possible formation of pyrazolo[3,4-*b*]pyridine **6** (Scheme 2). The whole carbon skeleton was assigned using ^{13}C NMR spectra, combining with DEPT and two dimensional ^{1}H, ^{13}C shift correlation HMQC and HMBC experiments.

We consider that compounds **5** result from a Michael-type nucleophilic addition of NH_2-group of aminopyrazole to C=C bond of compound **3** with intramolecular ring opening of the furane ring to give intermediate A (Scheme 3). Such intermediate can then evolve either by cyclization via attack of the nucleophilic nitrogen at the pyrazole to a carbonyl with elimination of a water molecule to form the obtained compounds **5**, or via attack of the C-4 at the pyrazole instead of the N-1 to give regioisomer **6**. The higher nucleophilicity[10b,19] of this nitrogen agrees with the findings (see Scheme 3).



Entry	R	Yield (%)
5a	CH_3	90
5b	$(CH_3)_3C$	92
5c	C_6H_5	85
5d	4-$CH_3C_6H_5$	87
5e	4-$CH_3OC_6H_5$	92
5f	4-$O_2NC_6H_5$	82
5g	4-ClC_6H_5	92
5h	4-BrC_6H_5	90

Scheme 2.



Scheme 3.

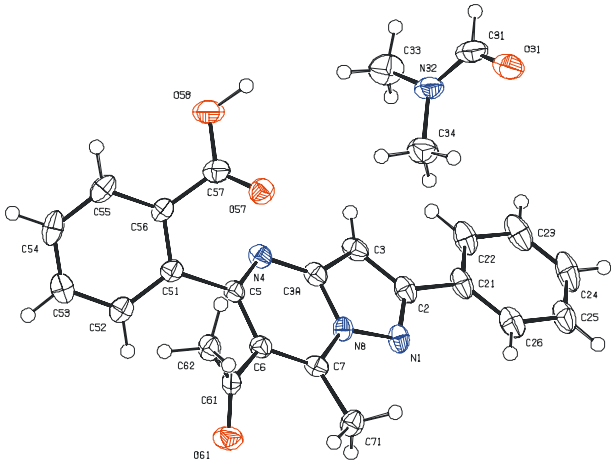


Figure 1. Molecular structure, showing 50% of probability ellipsoid, of one of the two residues that form the asymmetric unit for **5c**·**DMF**. Atom numbering is different from that used previously.

Structure of compounds **5** was established unambiguously by single-crystal X-ray crystallographic analysis of compound **5c** (see Fig. 1).

3. Conclusions

A simple, efficient and versatile one-step method for the synthesis of polyfunctionally substituted pyrazolo[1,5-*a*]-pyrimidines under solvent-free conditions is described. The use of a biselectrophilic reagent 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione has provided a highly regioselective cyclocondensation along with the introduction of a 2-benzoic acid residue that, because of their potential biological activity, may increase the scope and applications.

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18. *Preparation of 2-(6-acetyl-2-aryl-7-methylpyrazolo[1,5-a]-pyrimidin-5-yl)benzoic acids* **5a**–**h**: A mixture of equimolar amounts of 5-amino-3-R-1*H*-pyrazole **4** (1 mmol) and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione **3** (230 mg, 1 mmol) was heated in an oil-bath at 150 °C for 1.5–2 min. 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 the products formed were recrystallized from ethanol. Data for 2-(6-acetyl-7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)benzoic acid **5c**: This compound was obtained according to general procedure as white crystals. Mp 233–206 °C, yield 85%. IR (KBr) = 3252 cm^{-1} (OH), 1691 cm^{-1} (C=O), 1601 cm^{-1} (C=N); NMR 1H (DMSO-d_6, 400 MHz) $\delta = 2.07$ (s, 3H, CH_3-acetyl), 2.84 (s, 3H, 7-CH_3), 7.30 (s, 1H, H-3), 7.37 (d, 1H, H-3*Bz*, $J = 7.24$ Hz), 7.46 (t, 1H, H*p*, $J = 7.65$ Hz), 753 (t, 2H, H*m*, $J = 7.43$ and 7.65 Hz), 7.63 (t, 1H, H-5*Bz* $J = 7.44$ and 7.65 Hz), 7.68 (t, 1H, H-4*Bz*, $J = 7.24$ and 7.44 Hz), 7.98 (d, 1H, H-6*Bz*, $J = 7.65$ Hz), 8.11 (d, 2H, H*o*, $J = 7.43$ Hz), 12.97 (br, 1H, OH); NMR ^{13}C (DMSO-d_6) $\delta = 14.6$ (7-CH_3), 31.5 (CH_3-acetyl), 94.0 (C3), 122.5 (C6), 126.3 (C*o*), 128.9 (C*m*), 129.0 (C*p*), 129.3 (C5*Bz*), 129.9 (C3*Bz*), 130.1 (C6*Bz*), 131.3 (C1*Bz*), 131.6 (C4*Bz*), 132.3 (C*i*), 139.2 (C2*Bz*), 143.5 (C7), 147.7 (C3a), 155.9 (C5), 156.1 (C2), 167.7 (C=O, acid), 200.7 (C=O, acetyl); MS: (70 eV) m/z (%) = 371 (M^+, 57), 352 (19), 326 (100), 312 (91), 289 (18), 77 (65), 51 (29), 43 (38). HRMS: calcd for $C_{22}H_{17}N_3O_3$: $m/z = 371.1270$; found, 371.1284. Crystallographic data were collected at 120 K on a Bruker Nonius Kappa CCD area diffractometer using Mo-Kα X-ray radiation ($\lambda = 0.71073$ Å) and deposit at Cambridge Crystallographic data Center (CCDC reference: 642019). Main crystallographic data are following: Crystal system triclinic, space group $P\bar{1}$, unit cell dimensions: 11.629(2), 13.7910(13), 14.9390(19) Å, 83.537(7), 72.148(13), 88.153(11)°. Volume 2266.0(6) A^3; $Z = 6$, calculated density 1.303 Mg/m^3, $\mu = 0.09$ mm^{-1}; crystal size $0.25 \times 0.16 \times 0.15$ mm. Range of collection $3.10° < \theta < 27.50$ degr. Reflections collected/unique 51,198/10,342 [$R_{int} = 0.1318$]. 99.5% completeness to $\theta = 27.50$. Multi-scan absorption correction SADABS 2.0. $T_{Max}/T_{min} = 0.9866/0.9778$. Refinement with SHELXL-97 using a full-matrix least-squares on F^2; $S = 1.044$; $R_1 = 0.0967$, $wR_2 = 0.1566$. $W = [\sigma^2(F_o^2) + (0.0314P)^2 z + 6.12P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$.
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