Pergamon

Tetrahedron Letters 43 (2002) 9061–9063

TETRAHEDRON LETTERS

A novel product from the reaction of 6-aminopyrimidines and 3-formylchromone

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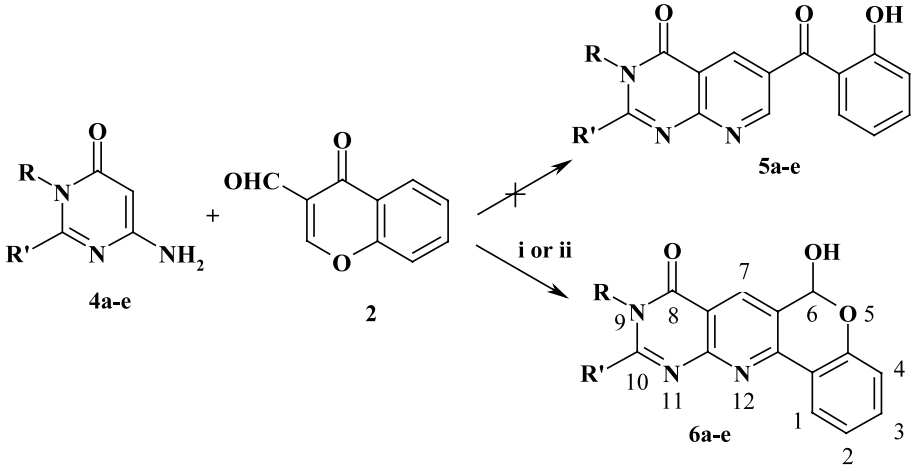
Received 8 October 2002; accepted 11 October 2002

Abstract—The reaction of 6-aminopyrimidines **4** with 3-formylchromone under microwave irradiation in dry media and classical heating in absolute ethanol afforded in all cases the unexpected 6-hydroxy-6,9-dihydrobenzopyranopyrido[2,3-*d*]pyrimidin-8-ones **6a–e** (alternatively named, 6-hydroxy-6,9-dihydro-5-oxa-9,11,12-triazabenzo[*a*]anthracen-8-ones). The structure of the final compounds was determined on the basis of NMR measurements, especially by $^{1}H,^{1}H$- and $^{1}H,^{13}C$ COSY, DEPT, HSQC, HMBC and NOESY.

1. Introduction

The pyrido[2,3-*d*]pyrimidines, deazaanalogues of pteridines, and their oxoderivatives have been of interest for their potential biological activities.[1] On the other hand, 3-formylchromone **2** has been used to prepare a variety of heterocyclic systems.[2] The reactivity of **2** towards several nucleophiles, as hydrazine, phenylhydrazine and particularly two functional nucleophiles (i.e. amidines, derivatives of guanidine and isothiourea[3] and aminopyrazole[4]), has been investigated.

Recently, we described a new synthesis of pyrazolo[1,5-*a*]pyrimidines, in the reaction of 3-formylchromone with aminopyrazoles (Eq. (1)), which occurred throught a Michael addition of the endocyclic nucleophilic nitro-



Scheme 1. (i) Microwave irradiation during 2–3 min under solvent-free conditions. (ii) Refluxing absolute ethanol during 2–3 h. R = H, CH_3; R′ = CH_3O, CH_3S, NH_2, OH, SH.

Keywords: 6-aminopyrimidine; 3-formylchromone; pyrido[2,3-*d*]pyrimidine; microwave irradiation.

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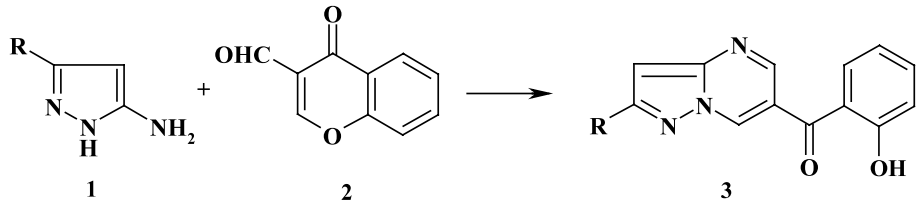
PII: S0040-4039(02)02316-X



(1)

gen of **1** with opening of the γ-pyrone ring of the aldehyde **2**.[4]

2. Results and discussion

Continuing with our studies on the synthesis of the pyrido fused rings, in this work, we investigated the behavior of 6-aminopyrimidines **4** in the reaction with 3-formylchromone **2**. Amines **4a–e** reacts with equimolecular amounts of 3-formylchromone **2** by reflux in absolute ethanol (2–3 h) or by microwave irradiation without solvent (2–3 min) to afford the unexpected pyrido[2,3-*d*]pyrimidines **6a–e** (Scheme 1),[5] but not the predicted pyridopyrimidines **5**, as observed in Eq. (1). The new compounds were obtained from moderate (in ethanol, 40–50%) to good yields (in microwave, 75–85%) as stable solids.

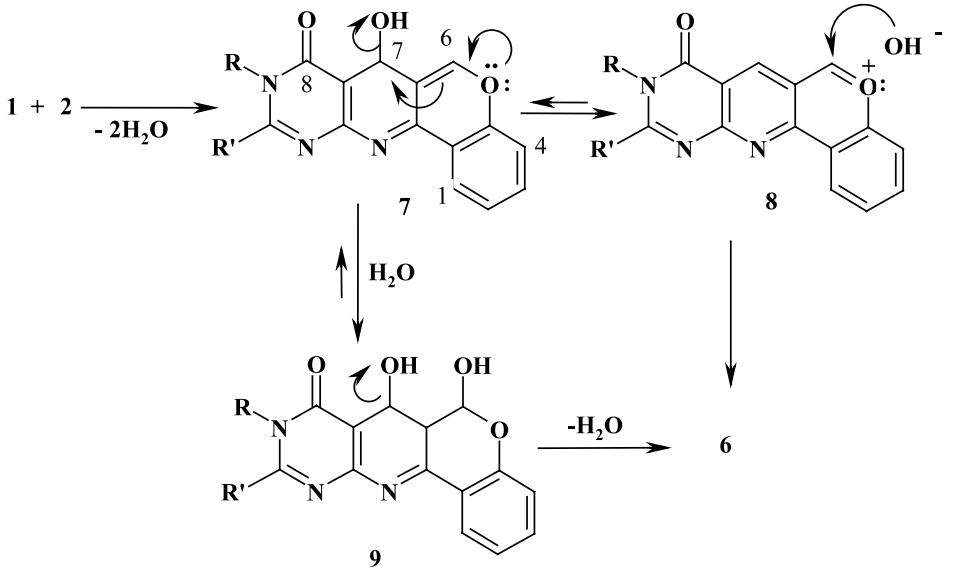
The cyclocondensation reaction of amines **4** with the aldehyde **2** gave regiospecifically the single pyrido[2,3-*d*]pyrimidines **6**, as determined on TLC. Based on ^{1}H and ^{13}C NMR, DEPT, COSY, HSQC, HMBC and NOESY techniques,[6] it was possible to assign all protons and carbon atoms of compounds **6** and to discard the isomeric structures **5**.

According to the results, we consider that compounds **6** initially result from the condensations of the carbon atom at position 5 and the 6-amino group of the pyrimidine **4** with the aldehyde and keto groups of the chromone **2**, respectively, throught termic rearrangements of the intermediate **7** (Scheme 2).

Once intermediate **7** is formed, it could either be converted into the pyrilium species **8** (stable by its completly aromaticity) or alternatively, to suffer a nucleophilic attack by a molecule of water (liberated in the previous step) at position 6, to afford the dihydroxy-derivative **9**. Both, **8** and **9** species could afford the isolated compounds **6**, by addition of the hydroxy ion (at position 6) or re-eliminating a water molecule, respectively, as shown in Scheme 2.

Although, proposed intermediate **7** should be the actual isolated compound, derivated from the double condensation reaction between **2** and **4**, we believe that the driving force to rearrange it into **6**, under the studied reaction conditions, is provided by the additional aromaticity gained in the pyridine ring of **6**. Apart from the all spectroscopical data, a strong three bonds coupling between the singlet of H-7 and 8-C=O is observed in the HMBC spectra, which is consistent with the proposed structures **6**, but not with structures **7**.

In conclusion, we have described in this paper the preparation of new pyrido[2,3-*d*]pyrimidines (in good yields) as unexpected products from the reaction of 6-aminopyrimidines and 3-formylchromone. This work is also a new example of the utility of microwaves in free-solvent organic synthesis.[7] Compounds **6** are particularly interesting owing to their high fluorescence (in



Scheme 2.

both solution and solid state), which will be studied in a future work to find its synthetic applicability.

Acknowledgements

The authors thank The Colombian Institute for Science and Research (COLCIENCIAS), UNIVERSIDAD DEL VALLE and 'Ministerio de Educación, Cultura y Deportes (Programa de Cooperación con Iberoamérica, AECI)' of Spain for financial support.

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5. *General procedure for synthesis of compounds* ***6a–e***. *Method A*: A solution of 1.40 mmoles of aminopyrimidine **4** and 1.40 mmoles of 3-formylchromone **2** in 25 ml of absolute ethanol, was refluxed during 2–3 h (TLC control). The reaction mixture was cooled. The cyclized products **6** were collected by filtration, washed with ethanol and recrystallized from DMF–water. *Method B*: Equimolar amounts of amine **4** and 3-formylchromone **2** were placed into pyrex-glass open vessels and irradiated in a domestic microwave oven for 2–3 min (at 600 W). Products **6** were treated with ethanol as described in method A.
6. All products gave satisfactory elemental analyses and spectral MS and NMR data consistent with their structures proposed. Data for representative compound follow. Compound **6a** ($R=CH_3$; $R'=CH_3O$): mp 250°C, yield 45% (Method A) and 75% (Method B); MS (70 eV) m/z (%): 313 (6), 312 (33), 311 (19, M^+), 310 (5), 294 (11), 284 (21), 283 (100), 282 (30), 255 (11); δ_H (300 MHz, DMSO): 3.39 (s, 3H, NCH_3), 4.10 (s, 3H, CH_3O), 6.60 (d, 1H, H-6, $^3J_{H\text{-}6\text{–}OH}=5.8$ Hz), 7.11 (dd, 1H, H-4), 7.19 (dt, 1H, H-2), 7.49 (dt, 1H, H-3), 7.72 (d, 1H, OH, $^3J_{OH\text{–}H\text{-}6}=5.8$ Hz), 8.29 (dd, 1H, H-1), 8.39 (s, 1H, H-7); δ_C (75 MHz, DMSO): 28.0 (CH_3N), 56.0 (CH_3O), 91.8 (C-6), 112.0 (C-7a), 118.0 (C-4), 120.8 (C-12b), 121.9 (C-2), 124.1 (C-6a), 125.1 (C-1), 132.6 (C-3), 134.2 (C-7), 151.5 (C-12a), 153.9 (C-4a), 156.0 (C-10), 157.0 (C-11a), 161.7 (C=O). Anal. calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.66; H, 4.28; N, 13.59%.
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