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Three-component synthesis of hexahydropyridopyrimidine–spirocyclohexanetriones induced by microwave

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Abstract—Pyridopyrimidine–spirocyclohexanetriones (**5**, **6**) and pyrimido[4,5-*b*]quinolinones (**8**) were obtained in a three-component microwave-assisted reaction of 6-aminopyrimidin-4-ones (**1**) with dimedone (**2**) and formaldehyde solution or paraformaldehyde, respectively. A mechanism is proposed based on the presence of a basic catalyst (triethylamine in this case) and the fact that single condensation intermediates are isolated prior to the cyclization leading to the final products.
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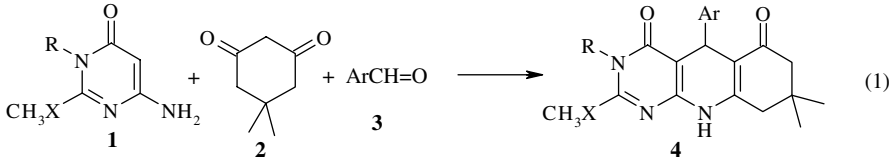
1. Introduction

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry. Over the last few years, there has been a tremendous development in three-component reactions and great efforts to afford new and effective MCRs.[1] Parallely, the potential application of microwave technology in organic synthesis,[2] and particularly under free-solvent conditions, is increasing rapidly because of its reaction simplicity, lesser environmental impact and reduced reaction time, providing rapid access to large libraries of diverse molecules.

The preparation of bioactive nitrogen containing heterocycles such as pyrido[2,3-*d*]pyrimidine derivatives, deaza-analogs of pteridines and their oxoderivatives is one of our ongoing projects due to their interesting bio-activities.[3] We have already reported some procedures for preparing fused dihydropyrido[2,3-*d*]pyrimidines,[4] including microwave-induced MCRs. Additionally, we have described a simple and efficient approach to prepare interesting biological[5] pyrimido[4,5-*b*]quinolines[4c] (**4**) in a three-component reaction from 6-aminopyrimidines (**1**), dimedone (**2**) and aromatic aldehydes (**3**) (Scheme 1).

Similarly, we report here an extension of the latter reaction using formaldehyde and microwave irradiation,



Scheme 1.

Keywords: 6-Aminopyrimidine; Formaldehyde; Dimedone; Pyrido[2,3-*d*]pyrimidine; Pyrimido[4,5-*b*]quinoline; Basic catalyst; Microwave irradiation.
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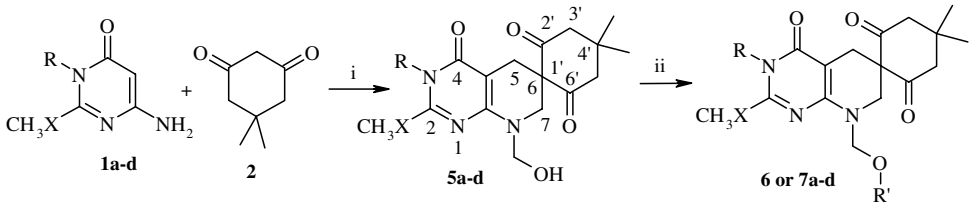


Comp.	5a	5b	5c	5d	6a	6b	6c	6d	7a	7b	7c	7d
R	H	H	CH_3	CH_3	H	H	CH_3	CH_3	H	H	CH_3	CH_3
X	S	O	S	O	S	O	S	O	S	O	S	O
Yield (%)	70	80	75	57	55	65	60	55	75	70	75	75

Scheme 2. Reagents and conditions: (i) excess of formaldehyde (37%) and microwave irradiation during 1–3 min; (ii) reflux in absolute ethanol or methanol.

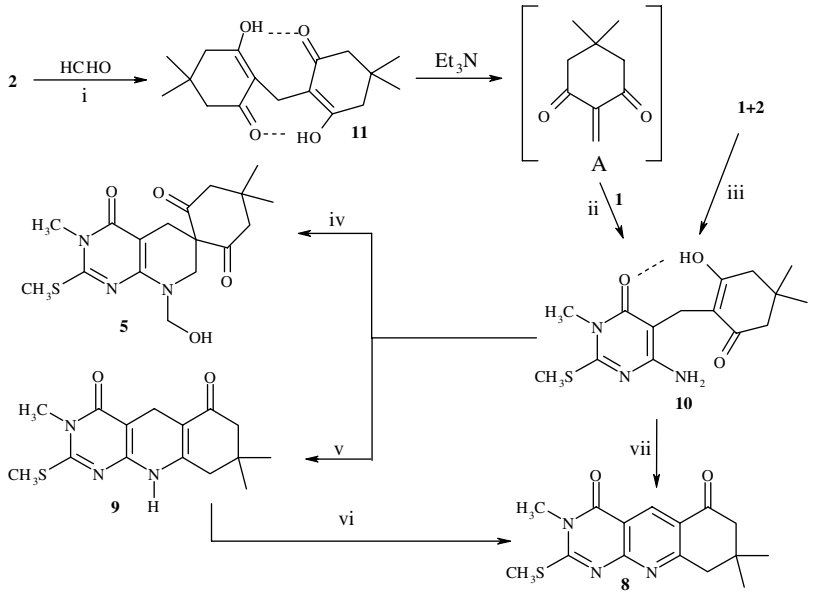
that renders, depending on the reaction media, either analogues of the reported pyrimido[4,5-*b*]quinolines (**4**) or the unexpected pyridopyrimidin-spirocyclohexanotriones.

2. Results and discussion

A facile three-component one-pot cyclocondensation takes place between 6-aminopyrimidines (**1**), dimedone (**2**) and formaldehyde affording pyridopyrimidin–spirocyclohexanetriones (**5a–d**) (Scheme 2). So, equimolar amounts of starting compounds **1** and **2** with a large excess of formaldehyde (37% in water) and triethylamine as catalyst were irradiated in a domestic microwave oven to give compounds **5** that were isolated in good yields (57–80%) (see Table 1 in Scheme 2); the reactions were repeated in different domestic microwave ovens to prove reproducibility, and no significant deviation was found.[6] Treatment of compounds **5a–d** with hot absolute ethanol or methanol lead to formation of compounds **6a–d** and **7a–d**, respectively (Scheme 2).[7]

Analogous reactions with paraformaldehyde in equimolar amount to dimedone, instead of a large excess in aqueous solution, yielded pyrimido[4,5-*b*]quinolinone (**8**),[8] when the mixtures were irradiated during 3–4 min (Scheme 3). Irradiation of the mixture during 2 min or heating in refluxing ethanol for 1 h afforded the dihydropyrimido[4,5-*b*]quinoline (**9**),[9] which with further heating gives the oxidized **8** (Scheme 3).

To prove the mechanism shown in Scheme 3, intermediates **10**[10] and **11** were isolated and left to evolve in the reaction conditions yielding the expected products. Therefore, the isolation of such intermediates permitted us to assume that the mechanism leading to the formation of **5** or **8** proceeds via an initial formation of the 2:1 dimedone/formaldehyde adduct **11**, that goes to the Knoevenagel adduct intermediate **A**, which suffers



Scheme 3. Reagents and conditions: (i) stirred in EtOH at rt for 2 h; (ii) reflux in ethanol during 4 h or MW during 2 min; (iii) formaldehyde (37%) and Et_3N at reflux in EtOH during 4.5 h or MW during 2 min; (iv) MW during 2 min and formaldehyde (37%) excess; (v) MW during 2 min or reflux in AcOH during 30 min; (vi) MW (2 min) or reflux in ethanol during 1 h; (vii) MW during 3–4 min.

a Michael-type addition reaction of the nucleophile C-5 in 6-aminopyrimidine (**1**) leading to the formation of intermediate **10**. This intermediate could either undergo cyclocondensation with excess of formaldehyde yielding to **5** or cyclization with loss of a water molecule to render **8**. The reactions to verify the evolution of **10** were carried out either in a large excess of formaldehyde to give **5** in 65% yield or, in its absence, to afford **8** in 40% yield.[11]

When reactions were carried out with a large excess of aqueous formaldehyde but without Et_3N, a poor conversion was achieved resulting in a mixture of compounds **5** and **9**. Additionally, the formation of compound **11**, isolated as crystals, was observed in all cases.[12a] The intermediate **10** was also isolated by reaction of **11** and **1** with Et_3N as a catalyst. These findings confirm that the key step in this reaction is the base-catalyzed elimination of **11** into **A**, and corroborates our previous postulation.

The structures of all new compounds were established by the usual spectroscopic methods, and the isolation of single crystals for some compounds permitted us to corroborate the postulated structures by X-ray diffraction analysis.[10,12]

3. Conclusion

The reported three component one-step procedure is a simple, practical and very regioselective method for the preparation of novel hexahydropyridopyrimidine–spirocyclohexanetriones or pyrimido[4,5-*b*]quinolinones from 6-aminopyrimidones, formaldehyde and dimedone, monitoring the regioselectivity of the reaction by the purity of formaldehyde.

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6. Preparation of the 8-hydroxymethyl hexahydropyrido-[2,3-*d*]pyrimidine-6-spiro-1′-cyclohexane-2′,4,6′-triones (**5a–d**): Equimolar amounts of 6-aminopyrimidine **1** (2 mmol) and dimedone **2** (2 mmol), excess of aqueous formaldehyde (30 mmol) (37%) and Et_3N (0.5 mmol) were placed into pyrex-glass open vessels and irradiated in a domestic microwave oven for 1–3 min (at 600 Watts). The products were washed with cold ethanol and recrystallized from acetonitrile. Data for **5c**. White solid, mp 220 °C, (75%). ^{1}H NMR (300 MHz, DMSO): δ 0.79 (s, 3H), 1.05 (s, 3H), 2.62 (d, 2H), 2.51(s, 3H), 2.62 (s, 2H), 3.03 (d, 2H), 3.32 (s, 3H), 3.65 (s, 2H), 5.00 (d, 2H), 5.62 (t, 1H). ^{13}C NMR (DMSO): δ 14.2 (CH_3S), 23.2 (C-5), 26.9 (CH_3), 28.5 (CH_3), 29.3 (CH_3N), 30.6 (C-4′), 49.7 (C-7), 50.0 (C-3′ y 5′), 61.7 (C-6), 70.2 (CH_2OH), 90.0, 153.3, 158.5, 160.6 (C=O (4)), 205.9 (C=O). EIMS: *m/z*: 365 (M^+, 6), 347 (10), 335 (25), 318 (35), 251 (45), 250 (100), 88 (30), 55 (40). Anal. Calcd for $C_{17}H_{23}N_3O_4S{\cdot}H_2O$: C, 53.24; H, 6.57; N, 10.95; S, 8.36. Found: C, 52.71; H, 6.83; N, 11.05; S, 8.10.
7. Preparation of the 8-ethoxy (or methoxy)methylhexahydropyrido[2,3-*d*]pyrimidine-6-spiro-1′-cyclohexane-2′,4,6′-triones (**6** or **7**): Products **5** were heated to reflux in absolute ethanol or methanol, respectively, for 15 min. Data for **6c**. White solid, mp 280 °C, (60%) ^{1}H NMR (300 MHz, DMSO): δ 0.78 (s, 3H), 0.97 (s, 3H), 1.03 (m, 3H), 2.38 (s, 3H), 2.86 (s, 2H), 2.93 (d, 2H), 3.34 (m, 2H), 3.55 (s, 3H), 5.70 (s, 2H). ^{13}C NMR (DMSO): δ 14.4 (CH_3S), 27.0 (CH_3CH_2O), 27.3 (C-5), 27.6 (CH_3), 28.3 (CH_3), 29.5 (CH_3N), 46.9 (C-7), 50.2 (C-3′ and C-5′), 60.6 (C-6), 87.2, 153.5, 159.7, 160.1 (C=O(4)), 203.3 (C=O). EIMS: *m/z*: 393 (M^+, 27), 348 (100), 250 (30), 88 (79), 83 (58), 56 (44), 41 (87).
8. Preparation of the pyrimido[4,5-*b*]quinoline-4,6-diones (**8a–d**): A mixture of 6-aminopyrimidine **1** (1 mmol), dimedone **2** (2 mmol) and paraformaldehyde (2 mmol) along with triethylamine (0.25 mmol) was placed into pyrex-glass open vessels and irradiated in a domestic microwave oven for 3–4 min (at 600 Watts). Products were recrystallized from ethanol. Data for **8c**. White solid, mp 254 °C, yield 45%. ^{1}H NMR (300 MHz, DMSO): δ 1.09 (s, 6H), 2.66 (s, 3H), 3.05 (d, 2H), 3.29 (d, 2H), 3.49 (s, 3H), 8.70 (s, 1H). ^{13}C NMR (DMSO): δ 15.2 (CH_3S), 28.0 (CH_3), 30.5 (CH_3N), 32.6 (C-8), 46.3 (C-9), 51.3 (C-7), 112.7, 124.7, 135.1 (C-5), 158.1, 161.0, 165.4, 168.6 (C=O(4)), 196.2 (C=O). EIMS: *m/z*: 303 (M^+, 39), 288 (12), 258 (100), 229 (20), 173 (11).
9. Preparation of hexahydropyrimido[4,5-*b*]quinoline-4,6-diones (**9**): A mixture of 6-aminopyrimidine **1** (1 mmol), dimedone **2** (2 mmol), paraformaldehyde (2 mmol) and triethylamine (0.25 mmol) was placed into pyrex-glass open vessels and irradiated in a domestic microwave oven

for 1–2 min (at 600 Watts). Products were recrystallized from ethanol. Data for **9c**: white solid (30% yield), mp 229 °C. ^{1}H NMR (300 MHz, DMSO): δ 0.99 (s, 6H), 2.13 (d, 2H), 2.28 (d, 2H), 2.53 (s, 3H), 3.04 (s, 2H), 3.33 (s, 3H), 9.27 (s, 1H). ^{13}C NMR (DMSO): δ 14.2 (CH_3S), 19.5 (C-5), 27.8 (CH_3), 29.6 (CH_3N), 31.9 (C-8), 39.4 (C-7), 49.9 (C-9), 92.9, 104.9, 151.1, 151.5, 160.7 (C-4), 194.4 (C-6). EIMS: *m/z*: 306 (20), 305 (M^+, 97), 304 (42), 290 (100), 258 (42), 173 (26), 118 (28), 88 (84). Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 59.22; H, 6.43; N, 13.68; S, 10.03.

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