Microwave-mediated Regioselective Synthesis of Novel Pyrimido[1,2-a]pyrimidines under Solvent-free Conditions

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Introduction

In recent years there has been increasing interest in the design of alkyl 1,4-dihydropyrimidine-5-carboxylates (1,4-DHPMs) and related Biginelli-like compounds [1] which are presented as valuable substitutes [2] for the well known Nifedipine® and other 1,4-dihydropyridine drugs [3] clinically used in the treatment of cardiovascular diseases. That interest is illustrated, i.a., by the disclosure of elegant protocols involving solid phase synthesis approaches [4] as well as solvent-free preparations under microwave irradiation. [5]

The purpose of the present work is to extend the scope of those studies to 2-amino derivatives and especially to the evaluation of their synthetic potential for the construction of novel pyrimido[1,2-a]pyrimidines, a ring system that can be found in marine-derived natural products such as crambescidin [6] and batzelladine [7] alkaloids.

Results and Discussion

Preparation of the starting 2-amino-1,4-DHPMs

A recent paper of Milcent [8] describes the synthesis (Scheme 1) of alkyl 2-amino-4,6-diaryl-1,4-dihydropyrimidine-5-carboxylates (2) from alkyl 3-aryl-2-benzoylpropenoates (1) and guanidine in DMF and the presence of an inorganic base. That procedure affords the desired heterocycles within reaction times ranging from 8 to 48 hours but reported yields (not optimized) do not exceed 40 % because of a competitive reaction yielding dialkyl 2,4,6,8-tetraaryl-4,6-dihydro-1H-pyrimido[1,2-a]pyrimidine-3,7-dicarboxylates (3). As those bicyclic derivatives arise from Michael type condensations between two molecules of ester (1) and guanidine, we reasoned that their formation could perhaps be disfavoured when directly starting from arylaldehydes, ethyl benzoylacetate, and guanidine. That proposal could be verified as the three-component reactions enabled to obtain derivatives 2a - e within 3 hours in 75 to 90 % yield whereas formation of 3 was not detected.
Diamines are known to react with 3-formylchromone 4 to yield pyrimidines [9]. The reaction initially takes place on the formyl group and is followed by an intramolecular attack of the second amine function on the C-2 atom of the pyrone ring followed by opening of that ring (Scheme 2). In such a sequence, derivatives 2 are excellent candidates for the preparation of bicyclic systems but due to the presence of three nitrogen atoms in 2, formation of two isomeric substances (2-aryl or 4-aryl derivatives) may be foreseen as illustrated in Scheme 2.

Isomers 5 (2H) only are obtained (as indicated by the spectral data) when the reactants are heated in boiling ethanol for several hours. However, we felt unsatisfied with those experimental conditions and we decided to perform the reactions under microwave irradiation. [10] In that way, we isolated the same final products but advantageously in better yields, under solvent free conditions, and within a few minutes.
The situation is more complicated when derivatives 2 are allowed to react with diethyl (ethoxymethylene)malonate (7). Indeed, four series of isomeric pyrimido[1,2-a]pyrimidines can be formed (Scheme 3). Once again, when the reactions are conducted in boiling ethanol or under microwave irradiation, only one series of compounds is obtained. Their spectral data are indicating of a 6-oxo structure as found in 8 or 10 but we had no further argument to distinguish those isomers. Therefore we resorted to a X-ray analysis that revealed that the product formed by the interaction between 2c and 7 is the 4-(4-methoxyphenyl)-2-phenyl derivative 8c.
Reaction pathways

We have not been able to isolate the monodehydrated intermediates when reducing microwave irradiation times, nor by performing the syntheses in a solvent at reflux or at room temperature. Anyway, the structure of the final products indicates that they result from the nucleophilic attack of the exocyclic nitrogen atom on the formyl function of 4 and that the ring closure involves the N(3) nitrogen atom of the pyrimidine cycle. That situation parallels previous results indicating a greater susceptibility of the N(3) atom towards electrophiles, when compared to the N(1) atom. [1] Similarly, reactions performed from diethyl (ethoxymethylene)malonate involve the same exocyclic and N(3) nitrogen atoms of the starting heterocycles 2.

Let us mention that, in agreement with the experimental results, AM1 calculations on the model compound 2a (1,4- and 3,4-dihydro forms) reveal a greater electronic charge density on the nitrogen atom of the exocyclic amino group, followed by the N(3) atom, and finally the N(1) atom.

Conclusion

In this work, we demonstrated that ethyl 2-amino-4,6-diaryl-1,4-dihydropyrimidine-5-carboxylates (2) react regioselectively with 3-formylchromone or diethyl (ethoxymethylene)malonate to afford pyrimido[1,2-a]pyrimidines (5 and 8 respectively) which had not been previously described. Interestingly, we observed that those bicyclic derivatives can advantageously be prepared in a microwave oven and in the absence of organic solvent, thus contributing to the promotion of economical and environmentally friendly experimental procedures.

References


10. Informations about microwave-mediated organic synthesis may be found, i.a., on the following web sites: [http://www-ang.kfunigraz.ac.at/~kappeco](http://www-ang.kfunigraz.ac.at/~kappeco); [http://www.umh.ac.be/~orgafs](http://www.umh.ac.be/~orgafs)

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