Microwave-Assisted Synthesis of 9-Arylpurines

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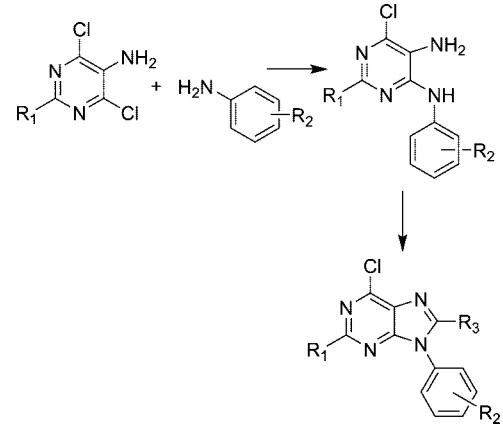
Received October 21, 2008

Purine derivatives are a continuous source of biologically active compounds and are thoroughly investigated as chemical biology tools and therapeutic agents. Their reported pharmacological activities involve protein kinases, adenosine receptors, microtubule assembly, etc., as exhaustively described in a recent review article.[1] Other purine applications that have also been recently reviewed include their properties as Hsp90 inhibitors,[2] their central role in neurotransmission and neuromodulation,[3] or their potential for the treatment of infectious diseases (i.e tuberculosis[4] or malaria[5]).

N^9 in purines is a critical substitution site for pharmacologically active compounds because in natural nucleosides that is the attachment point for (2-deoxy)ribose. Interestingly, 9-arylpurines and therefore their biological activities have been poorly investigated. Some recent examples where the biological activities of 9-arylpurines have been explored include agonists of the A_{2B} adenosine receptors,[6] ligands for the corticotropin-releasing factor receptor,[7] or substrates of the enzyme adenosine deaminase.[8] Moreover, 9-arylpurines are scarcely represented in some recently described purine libraries.[9,10]

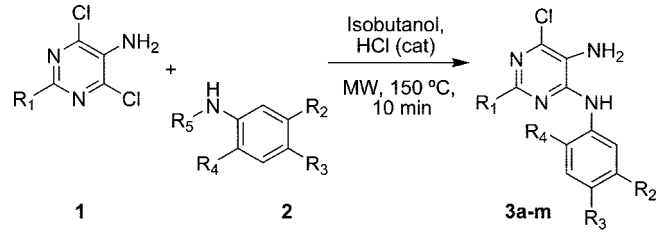
At least three methods have been described in the literature for the synthesis of 9-arylpurines. The direct nucleophilic aromatic substitution on purine rings[11] is limited to activated aryl halides. A broader application has been shown for the cross-coupling reaction of the purine base with arylboronic acid catalyzed by copper salts, initially described by Ding[12] and further studied by Gundersen[13] by adapting the general procedure of Chan,[14] Lam,[15] and Evans,[16] and recently reported by other laboratories.[10] Still there are several problems associated with this methodology, including difficulties in the isolation of the compounds,[12,17] the long reaction time required,[10,13,17] or the need of protection of some nucleobases to improve the fate of the reaction,[18] and, more significantly, in some cases, the poor yields reported.[10] As a third alternative, 9-arylpurines can be synthesized through the classical method that involves reaction of 5-amino-4,6-dihalopyrimidines with anilines, followed by a ring closing reaction.[19] This methodology is the most suitable to incorporate diversity at several points of the purine scaffold, as shown in Scheme 1. However, this strategy requires prolonged heating with the corresponding waste of time and energy, and the yields are variable. Therefore we consider that microwave assisted synthesis (MAOS) could constitute an interesting alternative to the classical heating step to perform the two-step synthesis described in Scheme 1. The advantages of MAOS in drug discovery have recently been reviewed.[20] A motivating precedent for our goal was found in the reaction between 4,6-dichloro-5-aminopyrimidine and a few anilines described by Hudson,[21] as the first step in their microwave-assisted synthesis toward pyrimidooxazepines.

Scheme 1. General Strategy for the Synthesis of 9-Arylpurines



As shown in Table 1, 4,6-dichloro-5-aminopyrimidine (**1**, R^1 = H) and its 2-methyl analogue (**1**, R^1 = CH_3) were microwave-irradiated in a Biotage Initiator 2.0 with an equimolar amount of different anilines (**2**, R^5 = H) in isobutanol in the presence of HCl at 150 °C for 10 min, to afford the 4-chloro-5,6-diaminopyrimidines **3a**−**3g** in good to excellent yields (entries 1−7). This short reaction time

Table 1. Synthesis of 4,5-Diaminopyrimidines by a Microwave-Assisted Reaction



1 **2** **3a-m**

entry	R^1	R^2	R^3	R^4	R^5	product	yield (%)
1	H	$COCH_3$	H	H	H	**3a**	74
2	CH_3	$COCH_3$	H	H	H	**3b**	95
3	CH_3	CH_2OH	H	H	H	**3c**	86
4	H	H	$COCH_3$	H	H	**3d**	66
5	CH_3	H	$COCH_3$	H	H	**3e**	85
6	H	H	OCH_3	H	H	**3f**	63
7	CH_3	H	OCH_3	H	H	**3g**	77
8	H	$N(CH_2CH_3)_2$	H	H	$COCH_3$[a]	**3h**	70
9	CH_3	$N(CH_2CH_3)_2$	H	H	$COCH_3$[a]	**3i**	91
10	H	$COCH_3$	H	OCH_3	$COCH_3$[a]	**3j**	50
11	CH_3	$COCH_3$	H	OCH_3	$COCH_3$[a]	**3k**	64
12	H	H	CH_3	H	$COCH_3$[a]	**3l**	55
13	CH_3	H	CH_3	H	$COCH_3$[a]	**3m**	70

[a] Entries 8−13, where R^5 = $COCH_3$, required a reaction time of 60 min.

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10.1021/cc800169d CCC: $40.75
Published on Web 01/29/2009

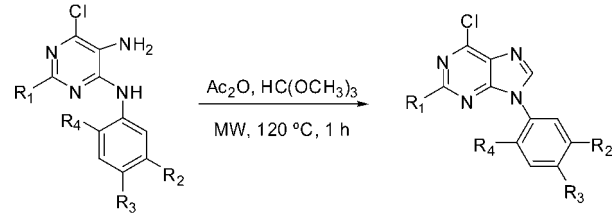
contrasts with previously described procedures requiring refluxing for about 8 h.[22,23] The presence of acid has been proposed to facilitate the nucleophilic displacement of the chlorine atom.[9,19] To broaden the scope of this reaction, we reasoned that acetamides could be used as starting materials in the above-described procedure because the presence of acid under the reaction conditions would promote the transformation of the acetamide to the corresponding amine[24] that in situ should react with the chloropyrimidine to afford the desired products. Indeed, different acetamides (Table 1, entries 8−13; $R^5 = COCH_3$) have also been successfully used as starting materials for the synthesis of the 4,5-diaminopyrimidines **3h**−**3m**, although a higher amount of HCl and longer reaction time (1 h) were required. In almost every case, the 4,5-diaminopyrimidines were isolated by direct filtration of the reaction mixture with high purity and were used as such in the next step without further purification. Yields were slightly higher for the 2-methylpyrimidines ($R^1 = CH_3$) compared to the corresponding 2-unsubstituted analogues ($R^1 = H$). When entries 1 and 2 are compared with entries 10 and 11, it can be deduced that the latter afforded lower yields, probably, because of to the presence of the OCH_3 at the ortho position of the phenyl ring. It is also worthy to mention that a variety of functional groups in the aryl moiety (CH_2OH, $COCH_3$, etc.) are fully compatible with the reaction conditions thus giving access to differently substituted 4,5-diaminopyrimidines.[25]

The next step consisted of the heterocyclization of the 6-chloro-4,5-diaminopyrimidines to the corresponding 6-chloropurines by treatment with orthoformates. According to the described procedure,[19] compound **3b** reacted with trimethyl orthoformate in acetic anhydride at reflux overnight to yield the cyclized product **4b** in 45% yield. Again, the use of microwave−assisted synthesis (MAOS) proved to be helpful. Thus, reaction under microwave irradiation of **3a**−**m** with trimethyl orthoformate in acetic anhydride at 120 °C for 1 h afforded the cyclized products **4a**−**m** with the yields reported in Table 2. The follow-up of the reaction course by HLPC/MS indicated that the imine formation with the orthoformate was very quick, while the cyclization toward the purine required longer reaction time. In our hands, under the MAOS conditions, one hour was the mean time required to obtain the purine compound as the major product, while in the literature the heterocyclization of 4,5-diaminopyrimidines requires refluxing for several hours.[7,19,26,27]

The 6-chloro-4,5-diaminopyrimidines **3** can be considered as versatile intermediates for the incorporation of different substituents at position 8 of the purine ring. To illustrate this point, the 4,5-diaminopyrimidines **3a** and **3b** were made to react with triethyl orthoacetate in acetic anhydride at 120 °C for 1 h, under MW irradiation, to afford the 8-methyl derivatives **5a** and **5b** in 70% and 51% yields, respectively (Scheme 2). Alternatively, the diaminopyrimidines **3a** and **3b** were transformed into their purine-8-one analogues[28] (**6a** and **6b**) by reaction with triphosgene in THF in the microwave for 20 min at 120 °C in excellent yields (Scheme 2).

Position 6 of the described compounds affords an additional site for ulterior modification. To illustrate this, compound **4b** was subjected to nucleophilic substitution reactions with amines also under microwave conditions. Thus reaction of **4b** with methylpiperazine, benzylamine, and *N,N*-dimethylethylenediamine in isopropanol in the presence of diisopropylethylamine (DIPEA) at 120 °C for 10 or 20 min (Scheme 3), afforded the 6-substituted purine derivatives **7a**−**7c** in 85%, 65%, and 70% yields, respectively.

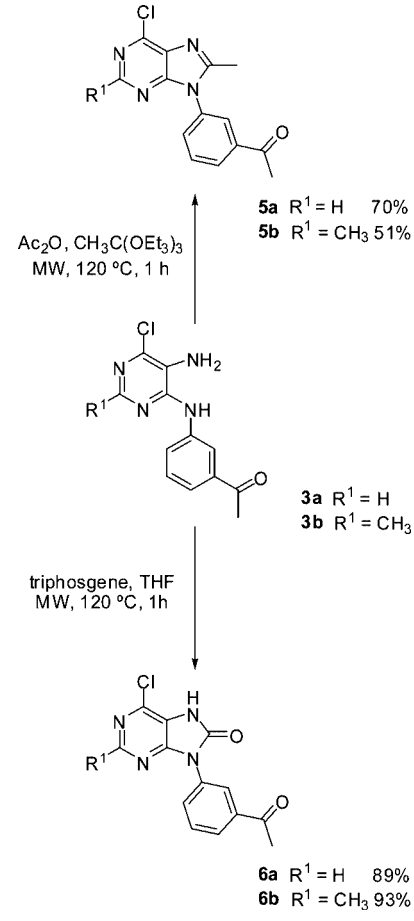
Table 2. Microwave-Assisted Cyclization Reaction of 4,5-Diaminopyrimidines



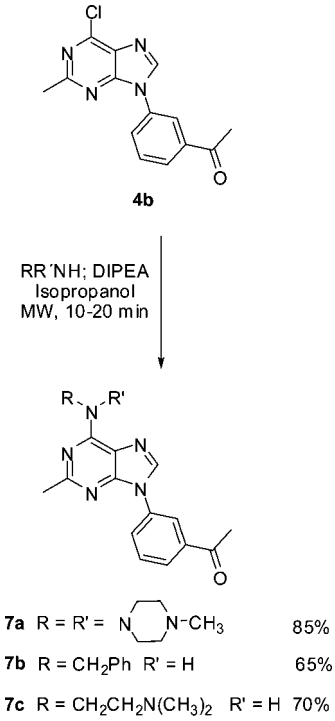
3a-m **4a-m**

entry	R^1	R^2	R^3	R^4	product	yield (%)
1	H	$COCH_3$	H	H	**4a**	62
2	CH_3	$COCH_3$	H	H	**4b**	52
3	CH_3	CH_2OH	H	H	**4c**	44
4	H	H	$COCH_3$	H	**4d**	50
5	CH_3	H	$COCH_3$	H	**4e**	61
6	H	H	OCH_3	H	**4f**	61
7	CH_3	H	OCH_3	H	**4g**	54
8	H	$N(CH_2CH_3)_2$	H	H	**4h**	56
9	CH_3	$N(CH_2CH_3)_2$	H	H	**4i**	50
10	H	$COCH_3$	H	OCH_3	**4j**	53
11	CH_3	$COCH_3$	H	OCH_3	**4k**	45
12	H	H	CH_3	H	**4l**	53
13	CH_3	H	CH_3	H	**4m**	47

Scheme 2. Microwave-Assisted Cyclization



Scheme 3. Microwave-Assisted Substitution Reaction



In conclusion, a general and highly versatile synthesis of 4,5-diaminopyrimidines under MAOS conditions has been described, and these diamines have been further used for the synthesis of different 6-chloro-9-arylpurines. The reaction conditions employed are fully compatible with different functionalities at the aryl moiety (CH_2OH, $COCH_3$, etc.), functions that could be subjected to further derivatization. The here described 6-chloropurines can be considered as excellent substrates for substitution reactions with N, O, or S-nucleophiles[29] or for C−C couplings.[30] Moreover, the purine-8-ones can be employed for access to a variety of 8-substituted purines.[28]

Acknowledgment. L.A. thanks the Spanish Ministerio de Educación y Ciencia for a FPU predoctoral fellowship. We thank Ms. María Nares for excellent technical assistance. This work has been supported by a grant of the Spanish CICYT (SAF2006-12713-C02-01).

Supporting Information Available. General procedures for the synthesis of compounds **3** and **4**, as well as analytical and spectroscopic data of the here described compounds (**3a**−**3m**, **4a**−**4m**, **5a**, **5b**, **6a**, **6b**, and **7a**−**7c**) are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC800169D