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Microwave-assisted synthesis of pyrazolo[3,4-*d*]pyrimidines from 2-amino-4,6-dichloropyrimidine-5-carbaldehyde under solvent-free conditions

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Abstract

The microwave-induced synthesis of pyrazolo[3,4-*d*]pyrimidines **4** in the reaction of N^4-substituted-2,4-diamino-6-chloro-5-carbaldehydes **3** with hydrazine is described here. Precursors **3** have been prepared by the mono-amination of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde **2** with aliphatic and aromatic amines. The reaction times with primary amines were relatively shorter than for secondary amines.

Keywords: Formylation; Vilsmeier–Haack reaction

The structural diversity and biological importance of pyrimidines have made them attractive targets for synthesis over many years. The pyrimidine is a widespread heterocyclic moiety, which is present in numerous natural products as well as synthetic pharmacophores with biological activities.[1] Substituted pyrimidines, particularly with amino-groups at 2 and 4 positions, are known pharmacophores in several structure-based drug design approaches in medicinal chemistry.[2] The 5-formylpyrimidines can be used as precursor in the synthesis of fused pyrimidine systems, among them we highlight the pyrazolo[3,4-*d*]pyrimidines, which are formed in several steps from a suitable pyrazole, or less frequently from a pyrimidine.[3] Pyrazolo-[3,4-*d*]pyrimidines are a class of heterocyclic compounds with very important biological properties.[4]

On the other hand, it has become widely accepted that many classical reactions under microwave irradiation perform better than reactions by conventional heating.[5,6] The microwave irradiation can be used to carry out a wide range of reactions in short times and with high yield and regioselectivity, without the need for solvents.[7] In the course of our research field aimed at the preparation of bioactive nitrogen-containing heterocycles, we addressed the synthesis of pyrazolo[3,4-*d*]pyrimidines. In this letter, we describe a versatile synthesis of N^4-substituted-4,6-diaminopyrazolo[3,4-*d*]pyrimidines **4** using microwave irradiation in the absence of solvent from N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes **3** in the reaction with hydrazine hydrate with good yields (Scheme 1 and Table 1). It is interesting to note that when this same reaction was carried out by conventional heating of aldehydes **3** with hydrazine hydrate, reactions preceded rather similarly rendering products **4** in equal yields. The only difference between those methods is that by microwave irradiation the reaction time is much shorter than by heating, 1 versus 30 min, respectively.[8]

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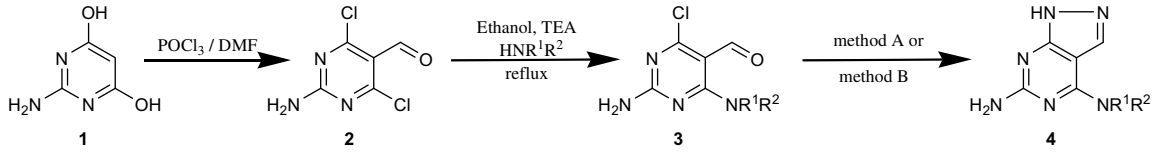


Scheme 1.

Table 1
Products of mono-amination of 4,6-dichloropyrimidine-5-carbaldehyde **3** and preparation of 4-substituted-pyrazolo[3,4-*d*]pyrimidines **4**

Entry	Amine	Compound **3**		Compound **4**	
		Mp (°C) ([a])	Yield (%)	Mp (°C)	Yield[b] (%)
1	*N*-Methylaniline	>180 dec	94	313–315	70
2	*N*-Ethylaniline	170–172 (166–169)	96	275–277	70
3	4-Methoxy-*N*-methylaniline	163–165	80	205–207	73
4	Aniline	209–211 (205–207)	80	296–298	70
5	*p*-Toluidine	202–204	75	271–273	93
6	3-Chloroaniline	233–235	85	289–291	60
7	4-Chloroaniline	226–228	80	296–298	60
8	4-Methoxyaniline	193–195	93	248–250	66
9	2-Methoxy-*N*-methylaniline	181–183	80	222–224	70
10	2-Methyl-*N*-methylaniline	183–185	80	265–267	80
11	*N*-Methyl-*p*-toluidine	176–178	80	270–272	60
12	4-Aminophenol	>300 dec	70	>300 dec	70
13	4-Aminobenzoic acid	>250 dec	70	>300 dec	80
14	Benzylamine	179–181	70	>250 dec	60
15	*N*-Phenylbenzylamine	165–167	70	257–259	80
16	*N*-Ethylbenzylamine	114–116	70	198–200	70
17	3,4-Dimethoxybenzylamine	160–162	80	282–284	80
18	*N*-Methylbenzylamine	169–171 (168–170)	40	221–223	90
19	*N*-Ethylbenzylamine	114–116	70	198–200	70
21	Dibenzylamine	160–162	40	234–236	50
22	2-(1*H*-Pyrrol-1-yl)aniline	202–204	60	233–235	77
23	Indoline	>185 dec	95	>300 dec	70
24	Diethylamine	131–133 (134–137)	70	259–261	40
25	Dimethylamine	189–191	80	>300	50
26	Dodecylamine	92–94	60	139–141	80
27	Cyclohexylamine	134–136	60	267–269	50
28	*N*-Methylcyclohexylamine	194–196	80	255–257	90
29	Piperidine	173–175	71	242–244	70
30	Pyrrolidine	178–180 (181–184)	54	287–289	50
31	Morpholine	176–178 (173–174)	81	228–230	87
32	2-(Piperazin-1-yl)ethanol	176–178	72	250–252	60

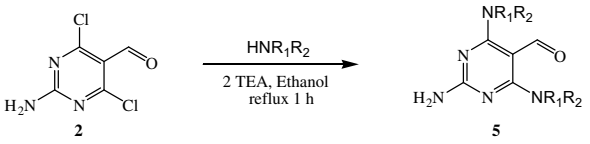
[a] Mp reported in the literature.[9]
[b] The yields reported were obtained by both methods.

4,6-Dichloropyrimidine-5-carbaldehyde **2** has been used as a functional starting material for the synthesis of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes, and due to the highly electron-deficient nature of the pyrimidine ring the nucleophilic aromatic substitution (S_NAr) allows us to introduce the amino group of different structures developing synthetic routes for the preparation of various 5-pyrimidinecarbaldehydes **3**.[9] Accordingly, we carried out the reaction of equimolar amounts of aldehyde **2** with a variety of amines, aliphatic, aromatic and heterocyclic, in a basic medium (triethylamine, TEA) under ethanol reflux (Scheme 1 and Table 1).[10]

As it can be seen from Table 1 all types of amines, including aliphatics, cyclic and alicyclic amines, aromatic, heteroaromatic and benzylic amines reacted readily well with 2-amino-4,6-dichloropyrimidine-5-carbaldehyde **2** to give the mono-substituted compounds **3** in good yields, which is controlled with equimolar ratio of reagent.

If instead of equimolar ratio, the amination of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde **2** was carried out in the presence of a double molar ratio of amine and TEA with respect to aldehyde **2**, the disubstitution product **5** was obtained (Scheme 2).[11,12]

The structure of all new compounds was determined on the basis of their analytical and 1D and 2D-NMR spectral data mainly, HR-MS, which are in agreement with their proposed structure. Single crystal X-ray diffraction analysis of compound **4** (entry 1, $R^1 = C_6H_5$, $R^2 = CH_3$) and **5** ($R^1 = H_3CC_6H_4$, $R^2 = CH_3$) was used to corroborate the postulated structures.[12]



Scheme 2.

We have prepared a variety of N^4-substituted-2,4-diamino-6-chloropyrimidine-5-carbaldehydes by monoamination with a variety of amines, when the nucleophilic mono-substitution is controlled with the molar ratio of reagent. These compounds are useful intermediates in the preparation of fused pyrimidine derivatives, such as pyrazolo[3,4-*d*]pyrimidines, which can be prepared also under microwave irradiation in the absence of solvent.

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8. *General procedure for the reaction of 2-amino-4-amine-6-chloropyrimidine-5-carbaldehydes with hydrazine monohydrate. Microwave method:* A mixture of compound (**3**) (0.2 mmol) and an excess of hydrazine monohydrate (0.5 mL) was subjected to microwave irradiation in the absence of solvent (maximum power 300 W during 1 min at a controlled temperature of 373 K) using a focused microwave reactor (CEM Discover). The solid products were collected by filtration and washed with ethanol and diethyl ether to give compound (**4**). Data for N^4-methyl-N^4-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-diamine **4** (entry 1, $R^1 = C_6H_5$, $R^2 = CH_3$), white crystalline solid, yield 70%, mp 313–315 °C. ^{1}H 400 MHz, DMSO-d_6, δ: 3.44 (s, 3H, CH_3), 5.61 (s, 1H, 3-H), 6.14 (s, 2H, NH_2), 7.55–7.38 (m, 5H, $H_{aromatics}$), 12.41 (s, 1H, NH). ^{13}C 100 MHz, DMSO-d_6, rt, δ: 38.0 (CH_3), 95.2 (C-3a), 128.0 (C_p), 128.3 (C_m), 130.0 (C_o), 132.8 (CH), 145.1 (C_i), 157.3 (C-4), 158.0 (C-7a), 161.7 (C-6). HR-MS calcd for $C_{12}H_{12}N_6$ 240.1123, found 240.1122. Anal. Calcd for $C_{12}H_{12}N_6$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.87; H, 5.74; N, 36.07.
Conventional method: A mixture of compound **3** (0.2 mmol) and an excess of hydrazine monohydrate (0.5 mL) in ethanol (5 mL) was heated under reflux for 30 min, then allowed to cool. The solid product was collected and washed with ethanol and diethyl ether to give the compound (**4**).
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10. *General procedure for the reaction of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde with amines.* A solution of 2-amino-4,6-dichloro-5-formylpyrimidine (**2**) (1 mmol), amine (1 mmol), and triethylamine (1 mmol) in EtOH (5.0 mL) was heated under reflux for 3 h. The solution was allowed to cool, and the product was filtered off, washed with EtOH, and air-dried. The times of reaction with primary amine were 1 h. Data for 4-(*N*-methyl-*N*-phenylamino)-2-amino-6-chloropyrimidine-5-carbaldehyde **3** (entry 1, $R^1 = C_6H_5$, $R^2 = CH_3$), yellow solid, yield 94%, mp >180 °C dec ^{1}H 400 MHz, DMSO-d_6, rt, δ: 3.40 (s, 3H, CH_3); 7.20 (m, 3H, H_m, H_p); 7.32 (t, 2H, H_o); 7.65–7.57 (s, 1H, and s, 1H for NH_2); 9.44 (s, 1H, CH=O). ^{13}C 100 MHz, DMSO-d_6, rt, δ: 41.0 (CH_3); 104.4 (C-5); 124.6 (C_m); 125.5 (C_p); 129.5 (C_o); 147.7 (C_i); 161.7 (C-4); 162.7 (C-6); 164.4 (C-2); 183.2 (CH=O). MS IE *m/z*: 264/263/262 (M^{2+}/M^{1+}/M^+, 39/35/94), 247/245(35/97), 210(21), 198(39), 156(22), 130/129(8/26), 107/106(10/41), 77(100), 52/51(18/63). Anal. Calcd for $C_{12}H_{11}ClN_4O$: C, 54.87; H, 4.22; N, 21.33; O, 6.09. Found: C, 57.11; H, 4.16; N, 21.45.
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