Unusual in Water Multicomponent Reaction of 3-Amino-5-methylpyrazole, Acetylacetone and Aldehyde

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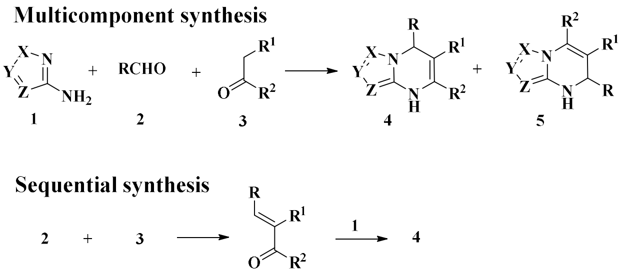
Multicomponent reaction of 3-amino-5-methylpyrazole, aliphatic aldehyde (paraformaldehyde or acetaldehyde) and acetylacetone in water by conventional heating, microwave or ultrasound activation undergoes on molar amounts of reagents 2:1:2, respectively, leads bis(2,5,7-trimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)-substituted methane or to corresponding 1,1-*bis*-substituted ethane.

Introduction

Use of multicomponent reactions to synthesize complicated heterocyclic compounds is a modern trend in organic chemistry allowing minimization of synthetic steps and increasing yield of target compound [1]. However, [illegible] approach can give unexpected results that are completely different from those obtained by more traditional multistep synthesis.

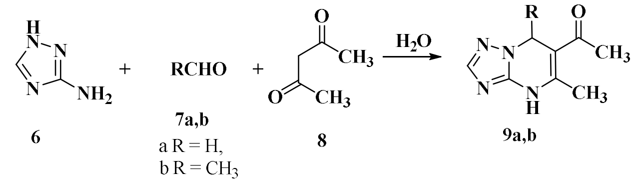
Azolopyrimidines having a nodal nitrogen are excellent objects for both, either multicomponent [2] or sequential synthesis [3] (Scheme 1); both of them presume use of diverse aminoazoles **1** (3-amino-1,2,4-triazole [4], 3-aminopyrazole [5], 5-aminotetrazole [6] etc) as a heterocyclization component. It is worth to note, exactly the multicomponent approach is gaining distribution last time, however, here is [illegible]ctivity loss due to realization of side processes in multicomponent system.



Scheme 1. Two approaches to synthesis of azolopyrimidines with a nodal nitrogen.

Another important trend in modern synthesis is “green chemistry” [7]; among its principles use of “green” solvents like water appeared to be highly effective [8].

In our recent publications [9, 10] we showed a possibility of obtaining azolopyrimidine in three-component way using 3-amino-1,2,4-triazole (**6**) and acetylacetone (**8**) as starting materials and water as solvent; the important feature of that research is use of formaldehyde (**7a**, [9]) or acetaldehyde (**7b**, [10]) as reagents (Scheme 2), whereas the majority of described data on azolopyrimidine synthesis presume use of exclusively aromatic aldehydes [3-6]. Application of aliphatic aldehydes allows to reduce molecular mass of target compounds and to satisfy the corresponding Lipinski criterion for biologically active compounds [11]. Typically, aminoazole with amidine moiety in multicomponent reaction with aldehyde and 1,3-dicarbonyl compound reacts with formation of pyrimidine ring, therefore, such process undergoes in three-component way similar to well-known Biginelli reaction.

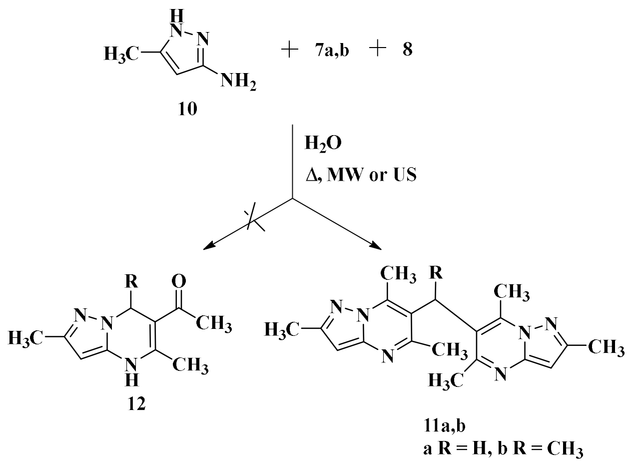


Scheme 2. Three-component in-water synthesis of 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines [9,10]

In the current research, we attempted to extend the application of multicomponent approach and to synthesize pyrazolo[1,5-*a*]pyrimidines using 3-aminopyrazole derivative and to check the scope and limitations of three-component in water synthesis concerning azolopyrimidines; however, our results here were somewhat unexpected.

Results and discussion

We studied the reaction of 3-amino-5-methylpyrazole (**10**), aldehydes **7a,b** and acetylacetone (**8**) in water and established the formation of single unusual product, namely bis(2,5,7-trimethylpyrazolo[1,5-a]pyrimidin-6-yl)-methane (**11a)** or 1,1-bis(2,5,7-trimethylpyrazolo[1,5-a]pyrimidin-6-yl)-ethane (**11b**), respectively (Scheme 3). Slight variation of the reaction conditions (using traditional heating as well as microwave or ultrasound activation) led to the same result: only compound **11** was isolated from the reaction mixture; the formation of “classical” dihydro derivatives like **12** was not observed even in trace.



Scheme 3. In water reaction of 3-amino-5-methylpyrazole (**10**) with aldehydes **7a,b** and acetylacetone (**8**)

Structures of **11a,b** were confirmed by their spectral data: EI mass spectra of **11a,b** showed molecule peaks that corresponded to participation of two molecules of **10** and **8** and only one molecule of **1** with loss of three molecules of water. ^{1}H NMR spectrum of **11a** showed signals of three methyl groups (2.31, 2.44 and 2.53 ppm, each had intensity 6 protons) and signal of pyrazole proton at 6.63 ppm (with intensity 2 protons) and signal of methylene group (4.00 ppm, two protons), which confirmed participation of compounds **10**, **7** and **8** on molar amount 2:1:2, respectively, and allowed to propose structure **11a** for the final product. Additionally, structures **11a,b** were consistent with obtained ^{13}C NMR data.

Naturally, yields of **4** were low when equimolar amounts of **10**, **7** and **8** were used for reaction; however, use of starting materials in stoichiometric amounts (2:1:2) allowed to obtain reasonable yields for **11a**, especially when microwave activation was applied; the best result (yield 65%) was obtained by ultrasound activation (Table 1).

Table 1. Yields of **11a,b** on different reaction conditions

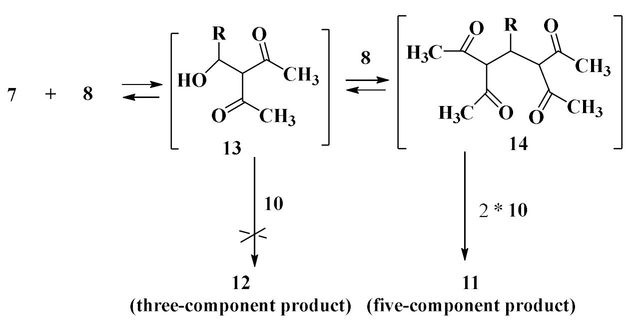
Compound	Yield, %		
	Method A[a]	Method B[a]	Method C[c]
11a	44	65	55
11b	-	40	35

[a]Conventional heating, 30 min

[b]Ultrasound activation, 25°C, 25-30 min

[c]Microwave activation, 25°C, 100 min

It seems, mechanism of the current reaction (Scheme 4) should include at least the formation of key intermediate **14**; the last one is formed evidently through the structure **13** which in turn is very likely responsible for possible formation of three-component product **12** (not observed in our case, however, is highly expectable in such kind of reactions [9,10], Scheme 2). Realization of different reaction pathway can be explained by equilibrium process between adducts **13** and **14** in water in the presence of a base; difference in basicity of amine **10** (3-aminopyrazole derivative **10** has higher basicity, than amine **6**) led to formation of unusual product, i. e. **11**.



Scheme 4. Possible mechanism of formation of **11a,b**.

Experimental part

Material and methods. The melting points of all compounds synthesized were determined with a Gallenkamp melting point apparatus. The NMR spectra were recorded at 400 MHz (100 MHz for ^{13}C) with a Varian MR-400 spectrometer. The EI MS spectra were measured on a GC-MS Varian 1200L (ionizing voltage 70 eV, direct input of the sample). Elemental analysis was realized on EuroVector EA-3000. Analytical samples of the compounds were obtained by their crystallization in water and further drying at room temperature. Microwave experiments were performed using the Emrys Creator EXP from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Sonication was carried out with help of standard ultrasonic bath producing irradiation at 44.2 kHz. Solvents, all reagents were commercially available and used without additional purification.

*Synthesis. General procedure for synthesis of **11a,b**.*

Conventional heating. A solution of 3-amino-5-methylpyrazole (**10**, 2.4 mmol), aldehyde **7** (1.3 mmol; paraformaldehyde (**7a**) or acetaldehyde **7b**) and acetylacetone (**8**, 2.4 mmol) in water (5 mL) was refluxed for 30 min. The crystalline product started to separate out during the reaction. The precipitate formed was filtered off, washed with water and air-dried.

Microwave activation. A solution of 3-amino-5-methylpyrazole (**10**, 2.4 mmol), aldehyde **7** (1.2 mmol) and acetylacetone (**8**, 2.4 mmol) in water (4 mL) was irradiated in MW reactor at 100 °C for 100 minutes. The precipitate formed was filtered off, washed with water and air-dried.

Ultrasound activation. A solution of 3-amino-5-methylpyrazole (**10**, 2.4 mmol), aldehyde **7** (1.2 mmol) and acetylacetone (**8**, 2.4 mmol) in water (5 mL) was continuously ultrasonicated at room temperature for 25-30 minutes. The crystalline product started to separate out either during the reaction. The precipitate formed was filtered off, washed with water and air-dried.

***bis*(2,5,7-Trimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)methane** (**11a**). White solid, mp 215-217 ºC (from ethanol). ^{1}H NMR (DMSO-d$_6$): δ 2.31 (6H, s, 2 CH_3), 2.44 (6H, s, 2 CH_3), 2.53 (6H, s, 2 CH_3), 4.00 (2H, s, CH_2), 6.63 (2H, s, 2 H-Pyrazol). ^{13}C NMR (DMSO-d$_6$): 13.3 (2 CH_3), 15.5 (2 CH_3), 16.7 (2 CH_3), 24.7 (CH_2), 105.9 (C-3, C-3'), 107.6 (C-6, C-6'), 144.6 (C-7, C-7'), 146.2 (C-3*a*, C-3*a*'), 152.4 (C-2, C-2'), 157.1 (C-5, C-5'). MS (EI, 70 eV): m/z (%) 334 (33) [$M^{+\cdot}$], 173 (23), 174 (99), 175 (13). Anal. Calcd for $C_{19}H_{22}N_6$ (334.19): C, 68.24; H, 6.63; N, 25.13 %. Found: C, 68.26; H, 6.66; N, 25.16%

6,6'-(Ethane-1,1-diyl)*bis*(2,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine) (**11b**). White solid, mp 148-150ºC (from ethanol). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.90 (3H, d, ^{3}J =

7.2 Hz, CH_3), 2.36 (6H, s, 2 CH_3), 2.45 (6H, s, 2 CH_3), 2.53 (6H, s, 2 CH_3), 4.75 (1H, q, ^3J = 7.6 Hz), 6.62 (2H, s). ^{13}C NMR (DMSO-d_6): 13.6 (2 CH_3), 15.8 (2 CH_3), 16.7 (2 CH_3), 21.8 (CH_3), 22.7 (CH), 104.5 (C-3, C-3'), 106.8 (C-6, C-6'), 143.8 (C-7, C-7'), 146.1 (C-3*a*, C-3*a*'), 152.4 (C-2, C-2'), 156.4 (C-5, C-5'). MS (EI, 70 eV): m/z (%) 348 (21) [$M^{+\cdot}$], 334 (21), 333 (100 M-CH_3), 188 (27), 187 (20), 174 (11). Anal. Calcd for $C_{20}H_{24}N_6$ (348.21): C, 68.94; H, 6.94; N, 24.12%. Found: C, 68.96; H, 6.98; N, 24.14%.

Conclusions

Multicomponent reactions of 3-amino-5-methylpyrazole with aliphatic aldehydes (formaldehyde, acetaldehyde) and acetylacetone in water undergo in five-component way with formation of *bis*-(6,6'-pyrazolo[1,5-*a*]pyrimidine-substituted methane and 1,1-*bis*-(6,6'-pyrazolo[1,5-*a*]pyrimidine-substituted ethane derivatives.

Acknowledgements

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