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Synthesis of Aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane in Water

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A synthesis of aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane from aromatic aldehyde and 3-methyl-1-phenyl-5-pyrazolin-5-one catalyzed by hexadecyltrimethyl-ammonium bromide in water is described. This method provides several advantages such as high yield, simple work-up procedure and environment friendly.

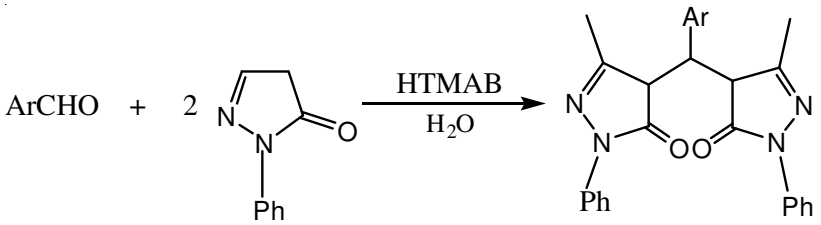
Key Words: Aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane, Aromatic aldehyde, 3-Methyl-1-phenyl-5-pyrazolin-5-one, Synthesis in water.

INTRODUCTION

The use of water as a solvent in organic chemistry was rediscovered in 1980s by Breslow[1] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Previously the scant solubility of the reactions was the main reason that ruled this solvent out from studies. Further reasons that make water unique among solvent are that it is cheap, not inflammable and non-toxic. In the past decade, there has been growing recognition that water is an attractive medium for many organic reactions not only for the advantage accorded by avoiding extensive drying reactants, catalyst and solvent, but also for the unique reactivity and selectivity that some times result[2,3]. However, water as a solvent was not frequently used until recently for several reasons such as many organic materials do not dissolve in water and many reactive intermediates and catalysts are decomposed in water. So it is necessary for adding some phase-transfer catalyst (PTC) or surfactant such as hexadecyltrimethylammonium bromide (HTMAB), tetrabutylammonium bromide (TBAB), 4-dodecylbenzenesulfonic acid (DBSA), because they benefit the organic materials uniform dispersion in water in course of synthesis. Based on our recent research, we have developed novel route for the synthesis of some heterocyclic compounds catalyzed by phase-transfer catalyst or surfactant in water[4,5]. Our important aim of this research is to synthesize more hetreocyclic compounds in aqueous media as well. The 3-methyl-1-phenyl-5-pyrazolone is very useful as a methylene active compound. It also had been widely used as analgesic, febrifuge, antibacterial etc. due to its useful biological and pharmacological properties[6]. Aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane is an important intermediate in

organic synthesis[7]. It had been reported for the synthesis of these compounds in the solid-state and under microwave[8]. Our interest in organic reaction carried out exclusively in water led us to investigate this compound through a simple route.

Hexadecyltrimethylammonium bromide (HTMAB) has been used in a number of organic reactions as a good phase transfer catalyst. However, the use of HTMAB as a catalyst in the synthesis of the aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane (**3**) has not been reported. In this manuscript, we wish to report a general and efficient route for the synthesis of this kind of compound using an inexpensive and commercially available HTMAB as catalyst. This is a one-pot combination in aqueous media, not only preserves the simplicity but also consistently gives the corresponding products in good to excellent yield (**Scheme-I**).



1 **2** **3**

Scheme-I

EXPERIMENTAL

Liquid aldehydes were distilled before use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on a Bruker Avance 400 (400 MHz) spectrometer using TMS as internal reference and $CDCl_3$ as solvent. Melting points are uncorrected.

General procedure: A mixture of an aromatic aldehyde (**1**) (2.0 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (**2**) (4.0 mmol) and HTMAB (50 mg) in water (20 mL) was stirred at 80 ºC for the length of time as indicated in Table-1. After the reaction is finished, the solid was filtered off and washed with H_2O (2 × 20 mL). The crude products were purified by recrystallization by $CHCl_3$ and MeOH to give **3**. Data of some compounds are shown below:

3b: IR (KBr, cm^{-1}): 1614, 1562, 1500, 1402, 1369, 1289, 835, 747, 690; δ 2.27 (s, 6H, $2CH_3$), 5.18 (s, 1H, CH), 7.21-7.33 (m, 4H, ArH), 7.39-7.46 (m, 5H, ArH), 7.68 (d, 4H, J = 8 Hz, ArH), 7.80~7.82 (m, 1H, ArH); Anal. calcd. (%) for $C_{27}H_{23}N_4O_2Cl$: C, 68.85; H, 4.92; N, 11.90. Found (%): C, 68.55; H, 5.02; N, 12.01.

3c: IR (KBr, cm^{-1}): 1600, 1500, 1422, 1296, 1100, 1055, 780, 760, 690; δ 2.08 (s, 6H, $2CH_3$), 4.69 (s, 1H, CH), 7.06-7.10 (m, 3H, ArH), 7.23-7.26 (m, 3H, ArH), 7.30-7.3 (m, 4H, ArH); 7.49-7.52 (m, 4H, ArH). Anal. calcd. (%) for $C_{27}H_{23}N_4O_2Cl$: C, 68.85; H, 4.92; N, 11.90. Found (%): C, 68.69; H, 4.99; N, 12.12.

RESULTS AND DISCUSSION

When the reaction of aldehyde **1** and 3-methyl-1-phenyl-5-pyrazolone **2** was performed in water in presence of HTMAB at 80 ºC, high yield of products were obtained. The results are summarized in Table-1.

TABLE-1
SYNTHESIS OF ARYL-*BIS*(3-METHYL-1-PHENYL-5-PYRAZOLONE-4-YL)METHANE IN WATER

Entry	Ar	Time (min)	Yield (%)*	m.p. (ºC)	
				Found	Reported[7]
1	C_6H_5 **1a**	30	89	171-72	170-172
2	2-ClC_6H_4 **1b**	30	78	242-43	–
3	3-ClC_6H_4 **1c**	30	89	154-55	–
4	4-ClC_6H_4 **1d**	30	94	209-10	210
5	2,4-$Cl_2C_6H_3$ **1e**	60	88	236-37	231-233
6	3-$NO_2C_6H_4$ **1f**	40	86	153-55	154
7	4-$NO_2C_6H_4$ **1g**	40	91	232-33	229
8	4-HO C_6H_4 **1h**	30	93	154-55	150-152
9	4-$CH_3OC_6H_4$ **1i**	30	90	151-52	148
10	4- $CH_3C_6H_4$ **1j**	30	91	203-04	203
11	4-HO-3-$CH_3OC_6H_3$ **1k**	90	58	202-03	201
12	3,4-$(OCH_2O)C_6H_3$ **1l****	90	–	–	–

*Isolated yield; **No reaction.

As shown in Table-1, we can find a series of aromatic aldehydes **1** were reacted with **2** in the presence of HTMAB in water. The reactions proceed smoothly to afford the corresponding products **3** in good yield. The reactivity of **1** was affected by the nature of substituents on the aromatic ring. The groups on the *p*-position of the aromatic aldehydes containing electron-withdrawing groups and electron-donating groups were under this reaction conditions. It can be found that the aromatic aldehyde with two electron-donating groups lead to a lower reactivity in this reaction **1k** even this reaction can not be carried out if the aromatic aldehyde **1l** are used. It is suggested that the reason is they make the electron density on the methylene carbon too high to be attacked by nucleophile **2**. Taking the reaction of 4-chloro-benzaldehyde as an example, we investigate the effect of the catalyst reagents on the reaction. It was found that the HTMAB plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, the reaction could be carried out in the absence of HTMAB when the mixture **1d** and **2** in water at 80 ºC for 2 h, but it obtained poor yield (36 %). We have also studied the kind of catalyst for this reaction. Some other often used PTC or surfactant such as TBAB, DBSA, sodium dodecyl sulfate (SDS) was tested. The reaction yields to 72, 58 and 89 %, respectively. These data indicated that the HTMAB is the most suitable for this reaction.

In summary, a procedure for the preparation of aryl-*bis*(3-methyl-1-phenyl-5-pyrazolone-4-yl)methane catalyzed by HTMAB in aqueous media have been developed. This is a one-pot three-component condensation in water. It is noteworthy that the experimental procedure is very simple and strict anhydrous conditions are not required. Water solution is a clean and environmentally desirable system. No harmful organic solvents are used. In addition, high temperature is not needed. This report has proposed and demonstrated a new useful and attractive process for the synthesis of these compounds.

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