

HClO₄-SiO₂ catalyzed distinct protocol for the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles under solvent-free conditions

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ABSTRACT

A convenient and efficient protocol has been developed for the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles from S-methylisothiureas and acid hydrazides using HClO₄-SiO₂ under solvent-free conditions. This procedure provides an easy access to a library of 3-N,N-dialkylamino-1,2,4-triazole derivatives in fair to good yields.

Keywords: 1,2,4-triazole, 3-N,N-dialkylamino-1,2,4-triazole, HClO₄-SiO₂

INTRODUCTION

1,2,4-triazoles are known to exhibit a wide range of biological properties including antibacterial,¹ anti-inflammatory,² anti-viral,³ antitumor⁴ and anti-asthmatic activities.⁵ They have also been used as bioisosters of esters, amides and as dipeptidomimetics in a number of pharmacologically important molecules.⁶ Moreover, 3-N,N-dialkylamino-1,2,4-triazole scaffolds are found as ligands in several receptor antagonists such as Gherline receptor (GHs-1a), Human vasopressin receptor (Human V_{1A})⁷ and δ opioid receptor (DOP)⁸ etc. In the view of greater medical significance, a number of synthetic routes have been developed for the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles. Generally, 3-N,N-dialkylamino-1,2,4-triazole are synthesized by the cyclisation of N-amidrazones using Veihe's salt,⁹ and cyclization of S-methylisothiureas with acyl hydrazides, using AcOH or TFA.¹⁰ However, these methods suffered from the limitation of harsh conditions, tedious synthetic procedures

and unsatisfactory yields. Therefore, developing a mild and more general procedure to access 3-*N,N*-dialkylamino-1,2,4-triazoles is still highly desirable.

Materials and Methods

General information

The obtained products were characterized by ^{13}C NMR and ^1H NMR spectra, which were recorded on a Bruker Advance 400 spectrometer in CDCl_3 at 400 MHz and 100 MHz, respectively. The chemical shifts were referenced to signals at 7.26 and 77.0 ppm, respectively. Mass spectra were recorded on a Shimadzu LCMS-QP5050A spectrometer at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). LC-MS was obtained using electron ionization. Melting points were measured with a Buchi B-545 melting point instrument. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm. All substrates were purchased commercially without further purification and all solvents were dried with molecular sieves.

General experimental procedure for synthesis of *S*-methylisothiurea(2)

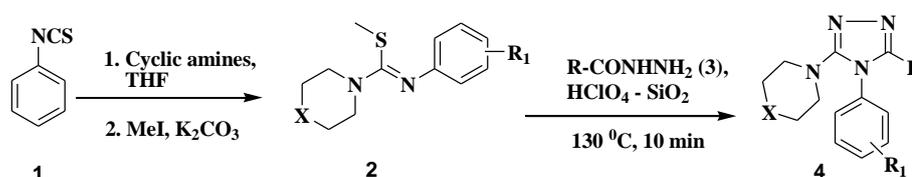
Morpholine or piperidine (1.2 mmol) was added to a solution of **1** (1.2 mmol) in THF (20 ml) at room temperature and stirred for 30 min. Then, K_2CO_3 (1.5 mmol) and methyl iodide (1.5 mmol) were added one after another to the mixture and stirred at room temperature for 6 h. After completion of reaction (Monitored by TLC), the reaction mixture was concentrated under reduced pressure and partition between EtOAc and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **2**. It was used as such in the next step without further purification.

General experimental procedure for the synthesis of 3-*N,N*-dialkylamino-1,2,4-triazoles (4)

A mixture of compound (**2**) (0.96 mmol), acid hydrazide (**3**) (1.50 mmol) and 20 mol % of $\text{HClO}_4\text{-SiO}_2$ was heated to 130 °C for 10 min. Then, the reaction mixture was cooled to room temperature, diluted with DCM (15 ml) and filtered. The supernatant DCM layer was washed with 2 N NaOH solution, dried over anhydrous MgSO_4 and concentrated under vacuum to afford **4** as a crude, which was further purified by column chromatography on silica gel using CHCl_3 and MeOH (9:1) as eluents.

RESULTS AND DISCUSSION

In recent years, heterogeneous catalysts are gaining more importance due to environmental factor. They have successfully been utilized in several organic transformations to minimize undesirable waste causing environmental pollution. To the best of our knowledge, no report has been reported for the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles using heterogeneous catalysts. In view of the above and as a part of our endeavours towards the development of new efficient synthetic methodologies for potential molecules,¹¹ herein, we have reported an efficient protocol for the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles from *S*-methylisothiourreas and acid hydrazides in the presence of silica-supported perchloric acid ($\text{HClO}_4\text{-SiO}_2$)¹² at 130 °C under solvent-free conditions (Scheme 1).



Scheme 1. Synthesis of 3-N,N-dialkylamino-1,2,4-triazoles

Initially, we have synthesized various *S*-methylisothiourreas (2) from substituted thiocyanates (1.2 mmol) (1) and secondary amines (morpholine and piperidine) (1.2 mmol) followed by treating with methyl iodide (1.5 mmol) and potassium carbonate (1.5 mmol). The conversion proceeded at room temperature and the reaction took place within 6 h to afford the desired product (2) in moderate to excellent yields (Table 1).

Table 1. Synthesis of *S*-methylisothiourreas

Entry	R1	Product	Yield (%) ^a
1	Ph	2a	91
2	4-MePh	2b	80
3	2-ClPh	2c	85

^aIsolated yield after column chromatography

After the successful synthesis of *S*-methylisothiourreas, we focused our attention towards the synthesis of 3-N,N-dialkylamino-1,2,4-triazoles (4). To initiate our study, the reaction of *S*-methylisothiourrea (2a) with acid hydrazide (3a) was chosen as a model reaction in the presence of catalytic amount of HClO₄-SiO₂ at 50 °C under solvent-free conditions.

Table 2. Optimization reaction conditions to **4a**

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (min)	Yield (%) ^a
1	HClO ₄ -SiO ₂ (20)	--	50	240	30
2	HClO ₄ -SiO ₂ (20)	--	80	200	42
3	HClO ₄ -SiO ₂ (20)	--	100	25	48
4	HClO ₄ -SiO ₂ (20)	--	130	10	88
5	HClO ₄ -SiO ₂ (20)	--	150	25	65
6	HClO ₄ -SiO ₂ (30)	--	130	25	88
7	HClO ₄ -SiO ₂ (40)	--	130	25	88

^aIsolated yield after column chromatography

We were delighted to observe the formation of desired product **4a**, albeit in a low yield of 30% after 4 h (Table 2, entry 1). Encouraged by this result, the temperature was gradually increased to 80°C, 100 °C and 130°C. Surprisingly, at 130°C, the reaction was completed within 10 min and yield of the product was 88% (Table 2, entry 6). When the reaction temperature was further increased to 150°C no improvement in the yield but a slight lowering in the yield was observed (Table 2, entry 7). Once we had established the suitable reaction conditions for the synthesis of 3-N, N-dialkylammino-1, 2, 4-triazoles and then we focused on the amount of catalyst. It was found that 20 mol% of HClO₄-SiO₂ was sufficient to carry out the reaction smoothly. An increase in the amount of HClO₄-SiO₂ more than 20 mol% showed no significant improvement in yield (Table 2, entries 6 & 7). We also examined the effect of various heterogeneous catalysts on reaction. It was found that HClO₄-SiO₂ showed high catalytic activity in terms of reaction times and as well as yield of the product (Table 3). The catalyst was recycled three times without the loss of activity.

Table 3. Effect of various catalysts on the synthesis of **4a**

Entry	Catalyst (20 mol %)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	CuSO ₄ -SiO ₂	--	130	10	30
2	H ₂ SO ₄ -SiO ₂	--	130	10	65
3	NaHSO ₄ -SiO ₂	--	130	10	40
4	PTSA-SiO ₂	--	130	10	55
6	HClO ₄ -SiO ₂	--	130	10	88

^aIsolated yield after column chromatography

Further, we have investigated the effect of various solvents on the reaction under reflux conditions. As it can be seen in Table 4, the solvents like DCM, THF and MeOH gave no positive effects, whereas the solvents like acetonitrile and dioxane correspondingly yields were 12% and 20 % (Table 4, entries 3, 4).

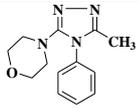
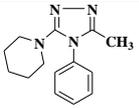
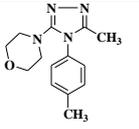
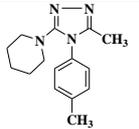
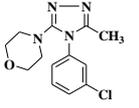
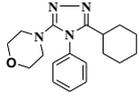
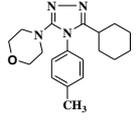
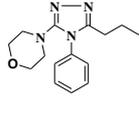
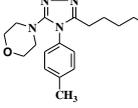
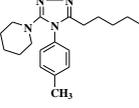
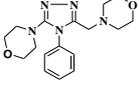
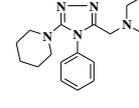
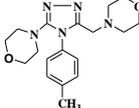
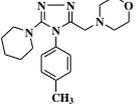
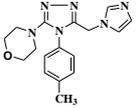
Table 4. Effect of various solvents in the synthesis of **4a**

Entry	Solvent	Temp (°C)	Time (Min)	Yield (%) ^a
1	DCM	reflux	10	--
2	THF	reflux	10	--
3	ACN	reflux	10	12
4	Dioxane	reflux	10	20
5	MeOH	reflux	10	--

^aIsolated yield after column chromatography

Subsequently, with the optimized conditions in hand, the scope of the reaction substrates was investigated. First we examined the reaction with substituted *S*-methylisothiourreas. It was found that all *S*-methylisothiourreas are reacted smoothly with acid hydrazides and gave the corresponding products in good yields and the results are listed in (Table 4). Next, we examined the reaction with acid hydrazides. The products were formed in high yields (80-89%) no additional solvent is required. All the synthesized compounds are well characterized by advanced spectroscopic analysis (¹H NMR, ¹³C NMR, and Mass spectroscopy).

Table 5. Synthesis of 3-N,N-dialkylamino-1,2,4-triazoles^a

			
4a, 88%	4b, 85%	4c, 85%	4d, 83%
			
4e, 84%	4f, 75%	4g, 77%	4h, 80%
			
4i, 82%	4j, 80%	4k, 77%	4l, 78%
			
4m, 75%	4n, 77%	4o, 77%	

^aIsolated yield after column chromatography

CONCLUSION

In conclusion, we have developed a simple, efficient and eco-friendly protocol for the synthesis of 3-N, N-dialkylamino-1, 2, 4-triazoles using $\text{HClO}_4\text{-SiO}_2$ as a heterogeneous catalyst. The mild, solvent-free conditions, short reaction times, high yields, operational simplicity and reusability of the catalyst are the notable advantages of the protocol.

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