Synthesis of triazolidines and triazole using DMAP

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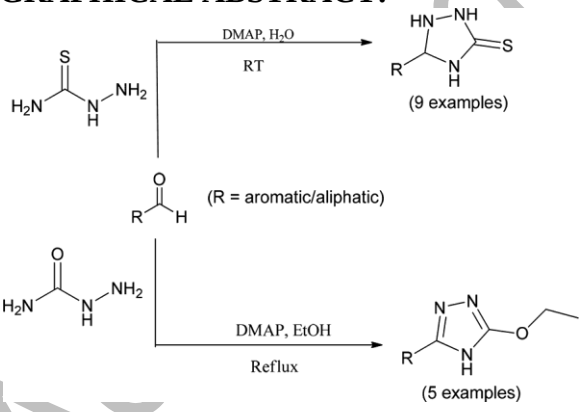
Abstract

An efficient methodology has been developed for the synthesis of 1, 2, 4-triazolidine-3-thione and 3-ethoxy-5-phenyl-4H-1, 2, 4 triazole using N, N-dimethylpyridine-4-amine (DMAP). Aldehydes and thiosemicarbazide reacted in water at ambient temperature in presence of DMAP and provided corresponding products in good to moderate yield.

GRAPHICAL ABSTRACT:



KEYWORDS: Aldehyde, Thiosemicarbazide/semicarbazide, Thiazolidine-3-thione, Triazole, DMAP

INTRODUCTION

Triazoles are important class of nitrogen containing heterocycles, because many of them exhibit interesting biological activities, such as anti-inflammatory,[1] antidepressant,[2] antifungal,[3,4] anticancer, anti-TB,[5,6] analgesic [7] and hypoglycemic.[8] Sulfur-linked 1,2,4-triazoles represent an important group in lead discovery. Also many sulfur-linked 1, 2, 4-triazole have been reported, as antibacterial,[9–11] antitumor, anti-HIV,[12] and anti-TMV (tobacco mosaic virus) activities.[13] Thus pharmacologically important sulfur-linked 1,2,4-triazole have attracted attention of many researchers to pursue novel, and easy synthetic routes. There are very few routes available for synthesis of these molecules. Recently, the synthesis of 1,2,4-triazolidine-3-thiones has been reported using $[C_{16}MPy]AlCl_3Br$ as reusable ionic liquid catalyst.[14] In another multi-component reaction 1,2,4-triazolidine-3-thione was synthesized from aldehyde, hydrazine hydrate, and trimethylsilyl isothiocyanate (TMSNCS) using sulphamic acid as a catalyst.[15] In continuation to our research work on synthesis of heterocyclic molecules using novel methodology, herein we report a novel system for the synthesis of 1,2,4-triazolidine-3-thiones which involves the reaction between aldehydes, thiosemicarbazides in the presence of catalyst N, N-dimethylpyridine-4-amine (DMAP) in water.

RESULT AND DISCUSSION

For our initial study we carried out reaction between anisaldehyde **(1)** and thisemicarbazide (**2)** in presence of N, N-dimethylpyridine-4-amine (DMAP) as a catalyst at room temperature in water (Scheme 1). After completion of reaction the desired product 5-(4-methoxyphenyl)-1, 2, 4-triazolidine-3-thione **(3e)** was isolated by filtration.

The reaction was also carried out, using different catalysts and results are summarized in Table 1.

It was observed that DMAP and PPTSA (*p*-toluenesulphonic acid pyridinium salt) are suitable catalyst for this reaction 20 mole %, DMAP is sufficient for this reaction. Further this reaction was also carried out in different solvents using 20 mole %, DMAP as a catalyst and it was noted that the reaction did not occur in toluene, dioxane, dichloromethane and chloroform but lower yield was observed when the reaction was carried out in ethanol. In the presence of DMF, THF and acetonitirle only Schiff base was isolated. Thus 20 mole %, DMAP as a catalyst and water as a solvent is optimal condition required for this reaction. As the product was isolated by just filtration, we tried to recycle the filtrate for above reaction and it was observed that the filtrate could be recycled up to five times and at the same time efficiency of the product also decreased as shown in Table 2.

This optimal reaction conditions were applied for the synthesis of various 1,2,4-triazolidine-3-thiones derivatives **(3a-i)** and results are summarized in Table 3.

It was observed that both electron withdrawing and donating substituted aryl aldehydes are suitable substrates for this reaction (Table 3, compounds 3b-3e). Heterocyclic aldehydes also undergo this transformation and gives corresponding products in high yield (Table 3, compounds 3g, 3h).

Further to extend the application of this methodology, we have taken semicarbazides **(4)** instead of thiosemicarbazide **(2)** and carried out the reaction but only Schiff base was isolated. It was observed that in the presence of ethanol and equivalent moles of DMAP, reaction yielded 3-ethoxy-5-phenyl-4H-1, 2, 4 triazole **(5e)** at reflux temperature after long reaction time (Scheme 2). We also tried other solvents instead of ethanol but no desired product was isolated.

This methodology is applicable for various aldehydes and results are summarized in Table 4.

CONCLUSION

In summary, we have successfully developed a novel, simple and efficient methodology for synthesis of 1,2,4-triazolidine-3-thiones and 1,2,4 triazoles. In this system, easily available aldehydes and thiosemicarbazide/semicarbazide were utilized in presence of DMAP in water/ethanol, to give good yields of the desired products after easy workup procedure

EXPERIMENTAL

General Procedure for Synthesis of 1, 2, 4-Triazolidine-3-Thione Derivatives (3a-i)

A mixture of (1 equiv.) aryl aldehyde, (1 equiv.) thiosemicarbazide and (20 mol %) DMAP in water were stirred at room temperature for 20-30 min. The progress of the reaction was monitored by TLC, and after completion of the reaction, the product is in the

form of precipitate was filtered and further purified by recrystalisation using EtOH as solvent or using silica gel column chromatography (EtOAc–Hexane).

5-Phenyl-1,2,4-Triazolidine-3-Thione (3a) [15]

White solid; m.p : 153-155 ^{o}C (lit. 154 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δppm 11.49 (s, 1H),9.47 (s, 1H), 7.83 (s, 1H), 7.63 (dd, *J* = 7.3, 2.2 Hz, 2H), 7.47 – 7.35 (m, 3H), 6.34 (s, 1H); FT-IR (KBr, cm^{-1}) 3388, 3232, 3149, 1597, 1532, 1460, 1444, 1368, 1289, 1226, 1098, 1059, 943, 870, 843, 759, 752 MS : $179(M)^{+1}$ (m/z).

General Procedure for Synthesis Of 3-Ethoxy-5-Phenyl-4H-1,2,4 Triazole Derivatives (5a-e)

A mixture of (1 equiv.) aryl aldehyde, (1 equiv.) semicarbazide (1.1 equiv) DMAP was stirred in EtOH at reflux temperature for 24-30 hr. The progress of reaction was monitored by TLC and after completion of the reaction, reaction mixture was concentrated under reduced pressure to give the crude product. The product was then purified using silica gel column chromatography (MeOH-DCM).

3-Ethoxy-5-Phenyl-4H-1,2,4-Triazole (5a) [17]]

White solid; m.p : 120 ^{o}C (lit. 121^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.69 – 7.64 (m, 2H), 7.36 (dd, *J* = 4.9, 1.7 Hz, 3H), 4.29 (q, *J* = 12.9, 6.3 Hz, 2H), 1.32 (t, *J* = 6.1 Hz, 3H); FT-IR (KBr, cm^{-1}) 3178, 3051, 1691, 1551, 1484, 1447, 1368, 1247, 1145, 1047, 1013, 953, 916, 875, 758, 690. MS : $190(M)^{+}$ (m/z).

ACKNOWLEDEMENT

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SUPPLEMENTARY DATA

The supporting material contains the spectral characterization data and copy ^{1}H and ^{13}C NMR spectra's. This material can be found via the "Supplementary Content" section of this article's webpage.

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Table 1. Synthesis of 1,2,4-triazolidine-3-thione **(3e)** using various catalyst [a]

Entry	Catalyst	Catalyst (moles %)	Yield (%)[b]
1	DMAP	10	82
2	DMAP	20	95
3	DMAP	30	95
4	PPTSA	10	85
5	PPTSA	20	87
6	PPTSA	30	90
7	L-Proline	10	60
8	L-Proline	20	65
9	L-Proline	30	67

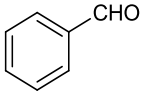
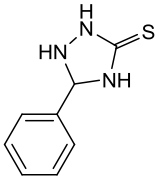
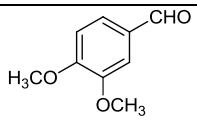
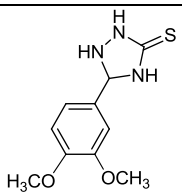
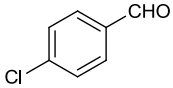
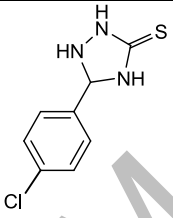
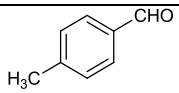
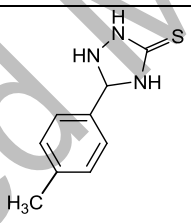
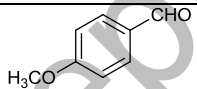
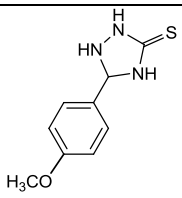
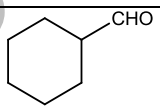
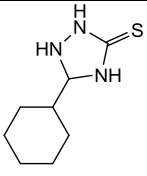
[a] Reaction conditions: 1.0 moles of anisaldehyde, 1.1 moles of thisemicarbazide in water at room temperature for 2 hrs. [b] Isolated yields after column chromatography.

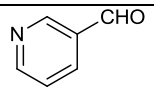
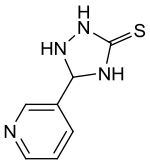
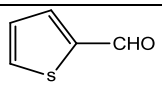
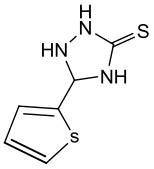
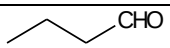
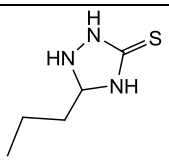
Table 2. Recycling of filtrate of DMAP [a]

Entry	No of Recycles [b]	Yield (%) [c]
1	Recycle 1	90
2	Recycle 2	90
3	Recycle 3	85
4	Recycle 4	80
5	Recycle 5	70

[a] Reaction conditions: 1.0 mole of anisaldehyde, 1.1 moles of thiosemicarbazide, 20 mole % DMAP in water at room temperature for 2hrs. [b] Product separated by filtration and in filtrate the reaction was carried without adding DMAP for 2hrs. [c]Isolated yields after column chromatography

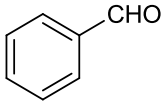
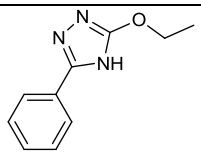
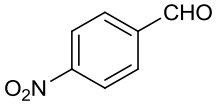
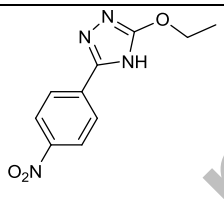
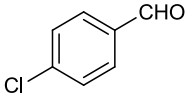
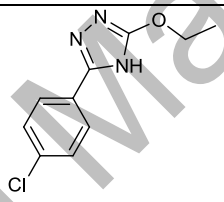
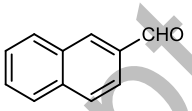
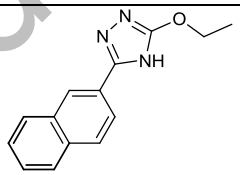
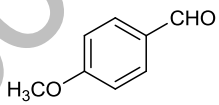
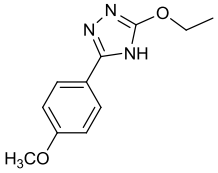
Table 3. Synthesis of 1,2,4-triazolidine-3-thiones using DMAP [a]

Compound	Aldehyde	Product	Time (Min)	Yield (%)[b]
3a			20	92
3b			25	90
3c			25	85
3d			30	90
3e			20	95
3f			25	88

3g			20	90
3h			25	85
3i			30	87

[a] Reaction conditions: 1.0 mole of aldehyde, 1.1 moles of thiosemicarbazide, 20 mole % DMAP in water at room temperature. [b] Isolated yields after column chromatography, and structures were confirmed by comparison of IR, ^{1}H NMR and mp. with literature reports [14-15]

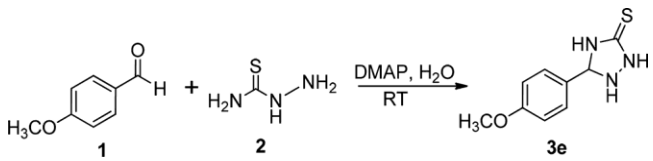
Table 4. Synthesis of various 3-ethoxy-5-phenyl-4H-1,2,4 triazole using DMAP in ethanol[a]

Compound	Aldehyde	Product	Yield (%)[b]
5a			78
5b			75
5c			68
5d			72
5e			80

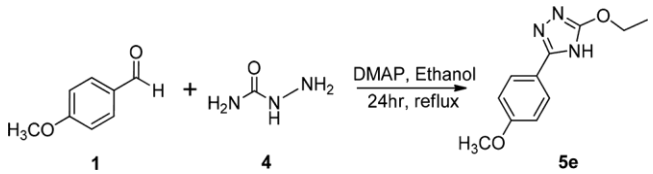
[a]Reaction conditions: 1.0 mole of aldehyde, 1.1 moles of semicarbazide, 1.1 mol of DMAP in ethanol at reflux temperature. [b] Isolated yields after column chromatography,

and structures were confirmed by comparison of IR, ^{1}H NMR and mp. with literature reports [16–17]

Scheme 1. Synthesis of 5-(4-methoxyphenyl)-1,2,4 triazolidine-3-thione using DMAP as catalyst



Scheme 2. Synthesis of 3-ethoxy-5-phenyl-4H-1,2,4 triazole using DMAP in ethanol



1 4 5e