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An efficient synthesis of 1,5-benzothiazepines in the presence of sub-stoichiometric amount of cyanuric chloride

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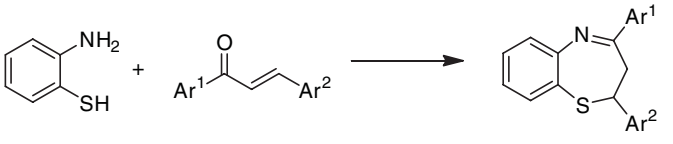
An efficient synthesis of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines has been developed by the reaction of various 1,3-diaryl-2-propenones with 2-aminothiophenol under thermal solvent-free conditions in the presence of a sub-stoichiometric amount of cyanuric chloride.



Keywords: 1,5-benzothiazepines; 2-aminothiophenol; cyanuric chloride; synthesis

1. Introduction

1,5-Benzothiazepines are important biologically active heterocyclic compounds which possess antifungal (*1*), antimicrobial (*2*), anticonvulsant (*3*), antibacterial (*4*), anti-human immunodeficiency virus (HIV) (*5*), Ca^{2+} channel antagonist (*6*), V_2 arginine vasopressin receptor antagonist (*7*), and HIV-1 reverse transcriptase inhibitor activities (*8*). The most common methods for the preparation of 1,5-benzothiazepines are the reactions of 2-aminothiophenol with α,β-unsaturated carbonyl compounds in the presence of $Yb(OTf)_3$ (*9*), nanocrystalline aluminum oxide (*10*), $Ga(OTf)_3$ (*11*), HBF_4-SiO_2 (*12*), sodium dodecyl sulfate (SDS) (*13*), $Mg(ClO_4)_2$ (*14*), $HClO_4$-SiO_2 (*15*), SmI_2 (*16*), and HCl (*17*). In view of the importance of the benzothiazepines, there still remains the necessity to develop a new methodology.

Cyanuric chloride 2,4,6-Trichlorotriazine (TCT) is a stable, non-volatile, inexpensive, and safe reagent which has been used synthetically for the preparation of various types of compounds such as 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones (*18*), bis(indolyl)methanes (*19*), *N*-sulfonyl imines (*20*), and 14-aryl or alkyl-14-H-dibenzo[*a*, *j*]xanthenes (*21*). In this paper, we wish to report a

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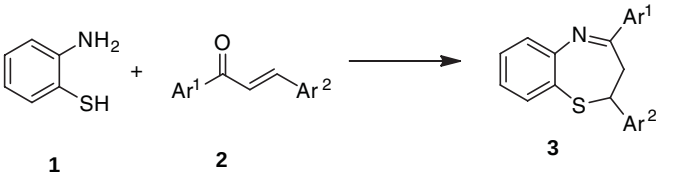
rapid and highly efficient method for the synthesis of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines in the presence of sub-stoichiometric amount of cyanuric chloride at 80°C (Scheme 1).



Scheme 1. Synthesis of 1,5-benzothiazepines using cyanuric chloride.

2. Results and discussion

To choose optimum conditions, the effect of temperature and the amount of TCT on the rate of the reaction was studied for the preparation of 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepine. Optimum conditions were observed at temperatures between 80°C and 90°C and a concentration of 5 mol%. When this reaction was carried out in the absence of TCT, thin layer chromatography (TLC) and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and corresponding thia-Michael adduct, the yield of the expected product was very poor.

In order to extend the above reaction (Scheme 1) to a library system, various kinds of 1,3-diaryl-2-propenones **2** (Table 1) were subjected to reaction with 2-aminothiophenol **1** to give the corresponding 2,4-diaryl-2,3-dihydro-1,5- benzothiazepine, and representative examples are shown in Table 1. All of the 1,3-diaryl-2-propenones, **2**, gave the expected products in high yields whether bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as the alkyl group). All of the structures were characterized by IR, ^{1}H NMR, and elemental analysis.

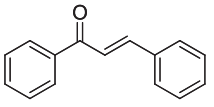
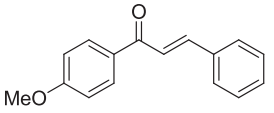
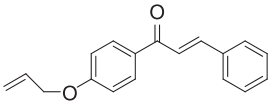
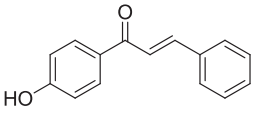
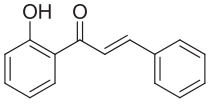
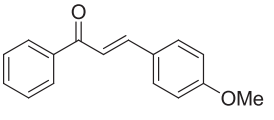
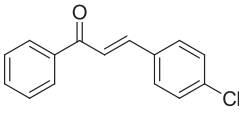
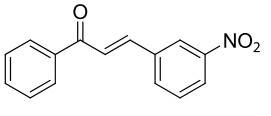
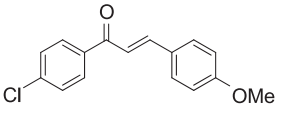
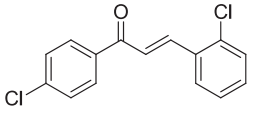
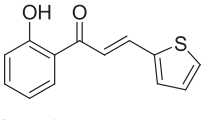
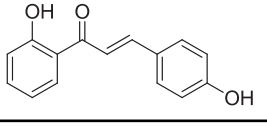
HCl generated *in situ*, from cyanuric chloride, efficiently catalyzes these reactions. Accordingly, cyanuric chloride (5 mol %) reacts with 'incipient' moisture and releases three moles of HCl and cyanuric acid (removable by washing with water) as a by-product. The *in situ*-generated HCl acts as protic acid and activates the carbonyl oxygen and forms a carbocation. Subsequent intramolecular nucleophilic attack by the NH_2 group on the carbocation followed by dehydration forms the 2,3-dihydro-1,5-benzothiazepines. The reaction could be facilitated by wet glass wares or by the presence of wet air. However, the reaction under dry reaction conditions in the presence of MS 4 Å met with failure. Thus, it amply indicates that the 'incipient' moisture plays an important role for HCl generation *in situ* from TCT.

To illustrate the efficiency of the proposed method, Table 2 compares some of our results with some of those reported for relevant reagents in the literature, which demonstrates its significant superiority. Compared with some of the reported methods in Table 2, the present method has a short reaction time, good yield, and solvent-free conditions.

3. Conclusion

In conclusion, we have established an efficient protocol for the synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines using inexpensive TCT. This method offers the advantage of shorter reaction times and easy workup. We believe that this methodology could be an important addition to the existing methodologies.

Table 1. Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines.[a]

Entry	1,3-Diaryl-2-propenones	Time (h)	Product	Yield (%)[b]	m.p. (°C) (reference)
1		4	**3a**	85	113–114 (114–115) (*22*)
2		5	**3b**	83	106–107 (104–107) (*22*)
3		5	**3c**	86	80–81 (78–80) (*22*)
4		5	**3d**	81	205–206 (200–204) (*22*)
5		5	**3e**	80	154–156 (154–155) (*11*)
6		3	**3f**	88	106–107 (106–108) (*22*)
7		3	**3g**	90	129–130 (127–129) (*22*)
8		3	**3h**	91	178–179 (178–180) (*22*)
9		5	**3i**	89	132–133 (130–132) (*22*)
10		5	**3j**	88	158–160
11		6	**3k**	79	88–89 (88–89) (*11*)
12		5	**3l**	82	171–172 (170–172) (*11*)

Notes: [a]Reaction conditions: 2-aminothiophenol (10 mmol); 1,3-diaryl-2-propenones (10 mmol), TCT (0.5 mmol); 80°C; neat.
[b]Isolated yield.

Table 2. Synthesis of of 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepine in comparison with other literatures.

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)	Reference
1	$Yb(OTf)_3$ (5 mol%)	[bmim][BF_4]	25	0.5	84	(*9*)
2	Nano-Al_2O_3 (3 mol%)	H_2O	110	12	71	(*10*)
3	$Ga(OTf)_3$ (10 mol%)	MeCN	60	4	30	(*11*)
4	SDS (10 mol%)	H_2O	100	12	65	(*13*)
5	TCT (5 mol%)	–	80	4	85	This work

4. Experimental

4.1. *General*

IR spectra were determined on FTS-40 infrared spectrometer; NMR spectra were recorded on Bruker AV-400 spectrometer at room temperature using TMS as an internal standard, and coupling constants (J) were measured in Hz; Elemental analysis were performed by a Vario-III elemental analyzer; Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used throughout without further purification unless otherwise stated.

4.2. *General procedure for the preparation of 3*

A mixture of the 2-aminothiophenol (10 mmol), 1,3-diaryl-2-propenones (10 mmol), and TCT (0.5 mmol) was stirred at 80°C using an electric mixer for the appropriate time (Table 1). Completion of the reaction was monitored by TLC. The material was cooled to 25°C, and after addition of water (50 mL) the mixture was stirred for 5 min. The solid so obtained was filtered off and purified by passing through a column of silica gel, eluting with 2% EtOAc in hexane to afford **3**. The structure of the products was confirmed by NMR, IR, and comparison with authentic samples obtained commercially or prepared by reported methods. The spectral data of some new 1,3-diaryl-2,3-dihydro-1,5-benzothiazepine are given below.

4.2.1. *2,3-Dihydro-2-(2-chlorophenyl)-4-(4-chlorophenyl)-1,5-benzothiazepine (**3j**)*

IR (KBr): υ 2926, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.02–7.70 (m, 10H), 5.29 (dd, $J = 4.8$, 12.8 Hz, 1H), 3.22 (dd, $J = 4.8$, 13.2 Hz, 1H), 2.90 (t, $J = 13.2$ Hz, 1H), 4.92 (s, 1H), 1.01 (s, 9H); Anal. Calcd for $C_{21}H_{15}Cl_2NS$: C 65.63, H 3.93, N 3.64, S 8.34; found: C 65.70, H 3.89, N 3.71, S 8.27.

Acknowledgements

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