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Note

Silica supported chromium trioxide: Microwave promoted oxidative ring closure of α-cyano-β-thioenaminones to isothiazoles

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Silica supported chromium trioxide is found to be an excellent reagent for oxidative ring closure of α-cyano-β-thioenaminones to isothiazoles in dichloromethane at room temperature or in dry media under microwave irradiation.

Keywords: Enamines, thioenamines, isothiazoles, oxidation, microwave promoted ring closure

IPC: Int.Cl.[8] C07D

Isothiazoles exhibiting a vast range of interesting chemical, biological and pharmaceutical properties represent a novel class of 1,2-azoles. Synthesis, properties and applications of isothiazoles have been reviewed extensively[1-3]. In addition, isothiazole derivatives are also known to possess muscaranic receptor activity and M 1 efficacy[4] and show good activity against polio 1 and ECHO 9 (ref. 5). Isothiazole derived penicillins and cephalosporins are found to be quite comparable with ampicillin[6]. Isothiazoles are also found to act as estrogen synthetase inhibitor[7].

Results and Discussion

A general synthesis of 3,5-disubstituted isothiazole-4-carbonitriles *via* oxidative ring closure of α-cyano-β-thioenaminones was recently reported[8]. In view of their easy availability[9] and simplicity of oxidative cyclization, thioenaminones appear to be an attractive precursor for synthesis of isothiazoles. The classical oxidative cyclization is generally carried out with reagents like *m*-chloroperbenzoic acid, hydrogen peroxide and halogens. In the search for new reagents it was decided to explore the efficacy of metal oxide reagents for oxidative cyclisation of thioenaminones as only one example involving SeO_2 was found in the literature[10].

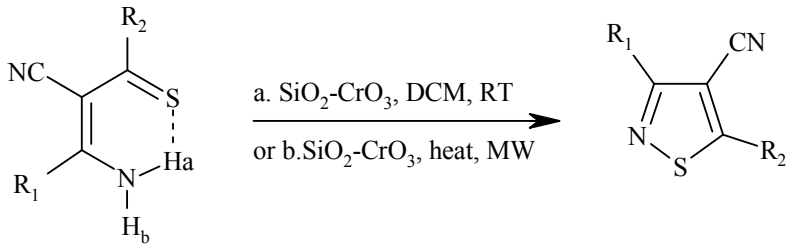
Chromium based reagents have found applications in synthetic organic chemistry as versatile oxidising agents[11,12]. A large number of chromium (VI) oxidants on solid support have been known and are found to be superior to other chromium oxidants[13]. Silica supported chromium trioxide found use in the selective oxidation of alcohols[14], aromatization of 1,4-dihydropyridine[15] and for regeneration of carbonyl compounds from the respective oximes[16]. Herein, a new application of this reagent for oxidative cyclisation of thioenaminones to isothiazoles in good to excellent yield is reported (**Scheme I**). Isothiazoles thus obtained were characterised through spectral analyses and are found to be identical in all respects with the compounds prepared previously by conventional method[8] (**Table I**).

Heterogeneous reactions involving microwave irradiation techniques[17,18] under dry condition provide distinct advantages in terms of clean products, short reaction time and easy work-up and have been successfully applied for synthesis of various heterocyclic systems[19] like aziridine, benzimidazole, 2-oxazolines, pyrazoles and substituted thiazole. However, preparation of isothiazoles under microwave irradiation is not reported. Thus, α-cyano-β-thioenaminones on treatment with SiO_2-CrO_3 oxidant under domestic micro oven irradiation in dry condition cleanly afforded the corresponding isothiazoles within 60-120 s in excellent yields. Results obtained from oxidative ring closure of thioenaminones by SiO_2-CrO_3 oxidant with or without solvent are reported in **Table I**.

In conclusion, use of SiO_2-CrO_3 oxidant for oxidation of thioenaminones to isothiazoles in excellent yields under microwave assisted solvent free condition demonstrates the usefulness of this reagent for synthesis of heterocycles. The short reaction times, ready availability of reagents and absence of aqueous work-up provide an attractive protocol for oxidative cyclization of thioenaminones to isothiazoles.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Hitachi 270-30 spectrometer. ^1H and ^{13}C NMR



1 **2**

Scheme I

Table I — Preparation of isothiazoles from thioenaminones at RT and by microwave irradiation

Entry	Compd[a]	R_1	R_2	RT		Microwave	
				Time (hr)	Yield[b] (%)	Time(s)	Yield[b] (%)
1	**2a**	CH_3	CH_3	2	79	60	80
2	**2b**	CH_3	CH_2CH_3	2.5	68	60	69
3	**2c**	CH_3	$CH_2CH_2CH_3$	2.5	70	120	72
4	**2d**	CH_3	CH_2O-C_6H_5	2.5	83	120	85
5	**2e**	CH_3	CH_2O-$C_6H_3Cl_2$ (2,4)	2.5	85	120	90
6	**2f**	CH_3	2-furyl	3	62	120	64
7	**2g**	CH_3	2-thienyl	2.5	74	120	75
8	**2h**	C_6H_4	CH_3	3	80	60	84
9	**2i**	*p*-MeO-C_6H_4	CH_3	3	82	60	85
10	**2j**	CH_3	$(CH=CH)_2$-Ph	3	73	120	74

[a] All products are known[8] and exhibit satisfactory spectroscopic and elemental data
[b] Yields of isolated products

spectra were obtained on a Bruker DPX-300, 300 MHz spectrometer using $CDCl_3$ as solvent. MS were obtained using a JEOL JMS 600 spectrometer.

Preparation of isothiazoles 2a-j

Method A. Thioenaminone (1 mmole) was dissolved in dichloromethane (10 mL) and SiO_2-CrO_3 reagent[19] (3 g, 6 mmoles) was added to it. The mixture was stirred for 2-3 h at RT and then filtered. The residue was washed with dichloromethane. The combined portions were concentrated and the solid mass was purified by recrystallization from ethyl acetate-pet ether.

Method B. Dry powder obtained from a well stirred mixture of thioenaminone **1e** (0.301 g, 1 mmole), dichloromethane (2 mL) and SiO_2-CrO_3 reagent (3 g, 6 mmoles) was irradiated in a microwave oven (BPL, 800 W output) for 120 s in an open beaker. The solid mass was washed with dichloromethane and filtered. Removal of the solvent gave the corresponding isothiazole **2e**.

Physical and spectral characterization data of compound **2e**: m.p. 145°C; IR (KBr): 3445, 2224, 1542, 1485, 1364, 1215 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.63 (3H, s, C=CCH_3), 5.47 (2H, s, CH_2), 6.95 (1H, d, *J* = 8.76 Hz, Ar-6′-H), 7.24 (1H, dd, *J* = 3 and 8.72 Hz, Ar-5′-H), 7.42 (1H, d, *J* = 2.43 Hz, Ar3′-H); ^{13}C NMR ($CDCl_3$): δ 18.13, 65.24, 107.5, 112.33, 115.22, 124.67, 127.85, 128.11, 130.55, 151.68, 167.96, 172.52; EI-MS: m/z (%) 298 (M^+, 27), 300 (24), 302 (7), 156 (100).

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