SHORT PAPER

J. Chem. Research (S),
2002, 601–603

Water promoted iodotrimethyl silane reactions: reductive cleavage of isoxazolidines and 2,1-benzisoxazoles to γ-amino alcohols and o-aminobenzophenones†

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Water promoted iodotrimethyl silane [ITMS] reductively cleaved isoxazolidines and 2,1-benzisoxazoles to γ-amino alcohols and *o*-aminobenzophenones respectively at shorter times and in higher yields at room temperature.

Keywords: water promoted iodotrimethylsilane, isoxazolidines, 2,1-benzisoxazoles

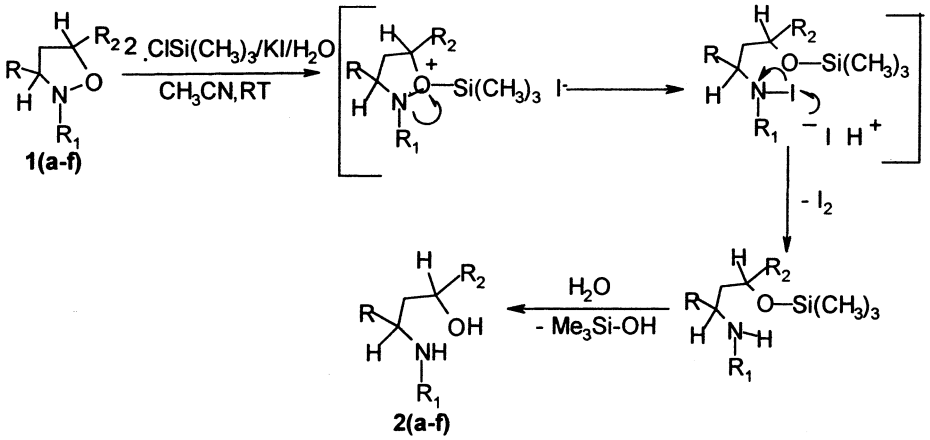
Organic reactions conducted in aqueous media have received much attention. Addition of stoichiometric or sub-stoichiometric quantities of water to a reaction mixture can result significant increase in reaction rate, yield and enantioselectivity. Also, water is an activator or co-activator of Lewis acid catalysed organic reactions.[1]

γ-Arnino alcohols are versatile intermediates in the syntheses of alkaloids,[2] carbohydrates,[3] amino acids[4] antibiotics,[5] *etc*. Recently, it has been reported that they are potential wide spectrum antidepressents.[6] Although there are numbers of methods reported[7] for the production of γ-amino alcohols yet efforts to find better reagents are still continuing.[6] However, these methods have limitations like the employment of costly metals *e.g.* Pd,[7b] Pt,[7c] Rh[7d] *etc*., use of low temperature and involvement of long reaction sequences,[6] contamination by side products,[8] *etc.*

Also, *o*-aminobenzophenones are key intermediates in the syntheses of clinically employed and biologically active 1,4-benzodiazepines [CNS drugs].[9] The reported methods for the synthesis of *o*-aminobenzophenones have their own limitations.[10] The classical methods require appropriately substituted anilines, high temperature reaction conditions and the corresponding *o*-aminobenzophenones are obtained in moderate yields.[9] The catalytic reduction of 2,1-benzisoxazoles uses expensive Pd[11] and groups susceptible to reduction do not survive. Reductive cleavage of 2,1-benzisoxazoles with $A1I_3$[12] and ITMS[13] requires extremely anhydrous conditions.

Iodo trimethylsilane (ITMS) is a versatile reagent in organic synthesis.[14] However, the potential of this reagent in heterocyclic synthesis or heterocyclic ring transformations is less explored and in particular heterocyclic ring transformation by ITMS promoted by water has not been reported. In continuation of our work on 2,l-benzisoxazoles[13,15] and isoxazolidines[16] and our research interests in reactions performed in hydrated media,[17] we now wish to report a mild and convenient method for the preparation of γ-amino alcohols and *o*-aminobenzophenones from isoxazolidines and 2,1-benzisoxazoles respectively by using ITMS promoted by water at room temperature.

Two equivalent quantities of ITMS [generated *in situ* from chloro trimethyl silane (CTMS) and potassium iodide] and 1 molar equivalent quantity of isoxazolidine **la** and half an equivalent amount of water (0.009 gm, 0.5 mmol) were stirred at room temperature for 0.5 h in acetonitrile and afforded **2a** in 95% yield. Similarly, the other compounds **2b–f** were prepared in excellent yields (Table 1). 2,l-Benzisoxazoles **3a–f** under the same reaction conditions produced *o*-aminobenzophenones **4a–f** in excellent yield. When 2,1-benzisoxazoles (R_3 = OCH_3 or OCO-CH_3) were reacted with ITMS/water the same product was obtained **4f** (Table 2, Scheme 2). It was observed that in the above reactions the rate of the reactions were tremendously



Scheme 1

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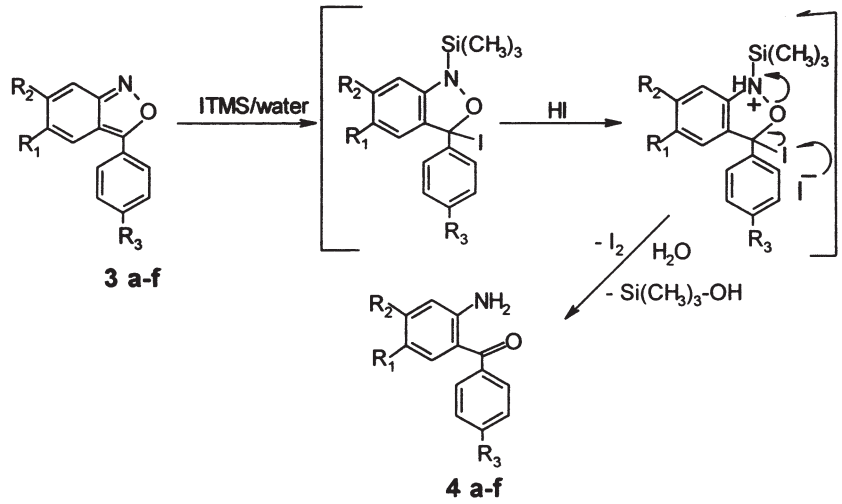
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Synthesis of γ-amino alcohols (**2a–f**)[a] with the ITMS/water system

Compound	R	R_1	R_2	Time/h ITMS/ ITMS +H_2O	Yield/% ITMS/ ITMS +H_2O	M.p/b.p.°C Reported/ found	C	H Calculated [found]	N
a	Ph	Ph	Ph	4/0.45	75/95	138–139/138	83.16 [83.11]	6.93 [6.85]	4.62 [4.55]
b	*p*-Me-Ph	Ph	Ph	3.5/0.50	65/85	117/116–118	83.28 [83.32]	7.25 [7.28]	4.41 [4.42]
c	2-Furyl	Ph	Ph	4.5/1.0	55/85	88/88–89	77.81 [77.78]	6.48 [6.35]	4.77 [4.70]
d	Ph-CH=CH-	Ph	Ph	5/1.20	70/90	108/106–108	83.89 [83.85]	6.99 [6.90]	4.25 [4.25]
e	Ph	Ph	CN	6/1.5	65/82	Gummy/gummy	76.19 [76.20]	6.34 [6.32]	11.11 [11.08]
f	*p*-Me-Ph	Ph	CN	5.5/1.45	50/80	Gummy/gummy	76.69 [76.56]	6.76 [6.72]	10.52 [10.49]

[a]All the compounds gave satisfactory IR, ^{1}H NMR and mass analyses and good agreement with authentic samples.[7e,16]



Scheme 2

Table 2 Synthesis of *o*-amino benzophenones by the ITMS/Water System

Products	R_1	R_2	R_3	Reaction time h ITMS[a]/ ITMS+ H_2O	Yield/% ITMS[a,b]/ ITMS+ H_2O	M.p/b.p.°C Found/ reported	C	H Calculated [found]	N
4a	Cl	H	H	2/0.2	92/98	99–100/98–100	67.38 [67.23]	4.31 [4.34]	6.04 [6.10]
4b	Br	H	H	2/0.25	90/97	110/110–111	56.52 [56.50]	3.62 [3.61]	5.07 [5.04]
4c	Cl	CH_3	H	3/0.40	85/95	121–124/122–124	68.43 [68.40]	4.88 [4.82]	5.70 [5.71]
4d	NO_2	H	H	4/0.50	91/99	1153/152–154	64.46 [64.42]	4.13 [4.10]	11.57 [11.52]
4e	MeCO	H	H	3/0.35	87/98	154–155/153–154	75.31 [75.30]	5.43 [5.45]	5.81 [5.81]
4f	Cl	H	OH	4/0.45	89/95	171–172/172–174	63.03 [63.01]	4.04 [4.06]	5.65 [5.55]

All the compounds gave satisfactory IR, NMR and mass analyses and mp's [a]The constants were compared with our authentic samples.[12] [b]The yields and time are compared with our previous results.

enhanced without side product formation. Acetonitrile was found to be the best solvent compared with dichloromethane and chloroform in terms of yield and reaction rate.

Regarding the mechanism of the reaction, it is proposed that ITMS first reacts at the oxygen atom of the isoxazolidine molecule which in presence of HI [generated *in situ*, from the reaction of ITMS and water which produced HI and ditrimethyl silyl) ether] liberates one iodine molecule and after treatment with water produced γ-amino alcohol by elimination of one molecule of trimethylsilanol. It was observed that no reaction took place when HI was reacted at refluxing temperature (Scheme 1). Also, it was found that when the amount of water was increased to more then half the equivalent of ITMS, the yield and rate of the reaction were found to be low. The reaction did not proceed at all when reaction involved chlorotrimethysilane alone.

In the case of 2,1-benzisoxazole, it is believed that ITMS first reacted with the electron rich nitrogen[18] and in the presence of the HI molecule gave a quatenary salt which liberated one molecule of I_2 and after aqueous work-up produced *o*-aminobenzophenones as shown below (Scheme 2).

The distinct advantages of the present system over the reported procedures are: (1) The reactions can be performed with the readily available reagent ITMS and water at room temperature with enhanced yields and shorter reaction times (2) It does not require anhydrous conditions or low temperature and products are obtained without contamination by side products. (3) Groups susceptible to reduction in the classical methods survive and work-up procedures are very simple.

In conclusion, we have demonstrated a new system, which offers a quick, convenient and inexpensive alternative to other methods for the production of γ-amino alcohols and *o*-amino-benzophenones.

Experimental

M.p.s were determined on a Buchi apparatus. Mass spectra were recorded with a Finnigan-MAT (INCOS 50) spectrometer. IR spectra were recorded on Perkin Elmer 237 B spectrophotometer and ^{1}H NMR spectra were recorded on a Varian T-60/90 MHz spectrometer. Commercially available (BDH) KI was used directly and chlorotrimethyl silane and acetonitrile were used after distillation. Isoxazolidines[7(e,g)16] and 2,1-benzisoxazole[9,12,13,19] were prepared as reported in the literature.

Typical procedure: Chlorotrimethyl silane (CTMS, 0.l60 g 2 mmol) and potassium iodide (0.300 g, 2 mmol) were stirred in acetonitrile (25 ml) at room temperature for half an hour. To this solution, isoxazolidine **1a** (0.301 g, l mmol) and water (0.009 g 0.5 mmol) were added and stirred for further 0.45 h at room temperature. The progress of the reaction was monitored by TLC. The solvent distilled off under *vaccuo*. The residine was treated with water (50 ml) and stirred for another half an hour before extraction with diethyl ether (50 × 2 ml). The organic layer was separated, washed with sodium thiosulfate solution (5%) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was crystallised from pet.- ether (40–60°C), to give **2a,** 0.273 g, Yield 95%, m.p.136–7 (lit.[6] 138°C) Mass (M+), 303; IR cm^{-1}, 1500, 1600, 3000, 3300, 3600 and ^{1}H NMR, (90 MHz, $CDCl_3$, δ ppm), 2,00 and 2.70 (both dt, 2H), 3.50 (1H, OH), 4.50 (q, 1H), 4.90(q, 1H), 6.50–7.40 (m, 14H, Ar-H, 1H, NH). Similarly, other compounds **2b–g** and **4a–f** were synthesised (Table 1 and 2).

The authors wish to acknowledge Dr J.S. Sandhu FNA, Director Regional Research Laboratory, Jorhat – 785006, Assam, and the Analytical Division for their keen interest in this work.

Received 19 November 2001; accepted 5 November 2002
Paper 02/1206

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