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EFFICIENT AND ECO-FRIENDLY SYNTHESIS OF SCHIFF BASES UNDER CATALYST FREE CONDITION

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ABSTRACT

An efficient and eco-friendly synthesis of N^1-(4-substitutedbenzylidene)-4-(tosylamino) benzo hydrazides (**2a-h**) having sulfonamido phrmacophore has been carried in PEG-400 as greener medium at room temperature. The titled compounds have been obtained in one pot by condensing 4-(toluene-4-sulfonylamino)-benzoic acid ethyl ester (**1**) with hydrazine and *in situ* formed acid hydrazide subsequently allowed to condense with aryl aldehydes. The route is found to be rapid, relatively economic and ecofriendly.

Key words: Efficient synthesis, Sulfonamide, Schiff bases, PEG-400, Mild reaction condition.

INTRODUCTION

Sulfonamides are an important class of biologically active compounds in organic and medicinal chemistry. The sulfonamide moiety is a crucial functionality because of its broad spectrum of pharmacological activities, such as high ceiling diuretic, antithyroid, antitumor, selective EP_3 antagonists[1,2] and anti-inflammatory[2] activities. Indeed, the sulfonamides are continue to play important role in chemotherapy in the combination of other drugs[3].

The chemistry of the carbon-nitrogen double bond plays a vital role in the progresses of chemical science[4]. Azomethine group (-C=N-) containing compounds typically known as Schiff bases form a significant class of compounds in medicinal and pharmaceutical

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chemistry with several biological applications that include antitumor[5,6], anticonvulsant[7], anti-HIV[8] and anti-inflammatory[9] activities.

Synthesis of schiff base is often carried out using acid or base catalysts and generally by refluxing the mixture of aldehydes (or ketones) and amines in organic medium[10-11]. The conventional method has been modified to obtain high yields of the schiff bases by using aprotic non-polar solvents[12,13], azotropic removal of water in a Dean-Stark apparatus, and by adding suitable dehydrating agents[14,15]. Environmentally benign synthetic methods have been receiving considerable attention and some solvent-free protocols have also been developed[16]. Synthesis of tetradentate schiff base under solvent-free and catalyst free condition using microwave irradiation has been reported[17]. Grinding together anilines and benzaldehydes yielded various kinds of benzylidene[18].

It was observed that the reported condensation methods are having one or other kind of drawback such as longer reaction times, high temperature, low yield, and media used are found to be carcinogenic and hazardous. In view of the above drawback, chemists are putting more efforts to modify the synthesis of schiff bases bearing sulfonamide employing efficient synthetic route using green tools.

Polyethylene glycol (PEG) is non-toxic, easily available, inexpensive, non-ionic liquid medium of low volatility and high stability in acidic and basic condition. PEG and its monoethyl ethers are thermally stable and reusable. The PEG-400 is widely used in many organic reactions for conversion[19] of oxiranes to thiiranes, asymmetric aldol reactions[20] in presence of L-prolin, cross-coupling reaction[21], PEG-400 also used as catalyst[22] and reaction medium for monobromination of aromatics using NSB[23].

Considering the synthetic utility of PEG, biological significance of sulfonamides and schiff bases, herein we have developed an efficient, ecosustainable, environmentally benign one pot synthesis of N^1-(4-substitutedbenzylidene)-4-(tosylamino) benzohydrazide in PEG-400 at room temperature.

EXPERIMENTAL

General procedures

All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR (JASCO FT-IR) Japan. The ^{1}H NMR was measured on Bruker DRX-300, 300 MHZ FT NMR with low and high temperature in

DMSO using TMS as internal reference. Mass spectra were recorded on an Ieo SX 102/DA-600 mass spectrometer.

Synthesis of N^1-(4-substituted benzylidene)-4-(tosylamino) benzohydrazide (2a-h)

4-(Toulene-4-sulfonylamino)-benzoic acid ethyl ester (0.002 mol) and hydrazine hydrate (6 mL) were dissolved in PEG (15 mL) and the reaction solution was stirred for 6 h. at room temperature after formation of acid hydrazide aromatic aldehyde (0.002 mol) was added and then the reaction mixture was further stirred for 4 h. The progress of the reaction was monitored on TLC plate using hexane: ethyl acetate (7 : 3). After completion, the mixture was poured into water and was extracted with EtOAc. The solvent was removed and crude product was subjected to column chromatography to obtained pure schiff bases. The PEG was recovered from the aqueous layer.

N'-(4-Hydroxybenzylidene)-4-(tosylamino) benzohydrazide (2b)

Yield 92%, m.p. 259-261^{o}C, IR (KBr, cm^{-1}): 3240, 3210, 1640, 1606, 1549, 1335 and 1160. ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.32 (s, 3H, CH_3), 7.01 (d, 2H, Ar-H *J* = 8Hz), 7.19 (d, 2H, Ar-H *J* = 8Hz), 7.37 (d, 2H, Ar-H *J* = 8Hz), 7.54 (d, 2H, Ar-H *J* = 8Hz), 7.69 (d, 2H, Ar-H *J* = 8Hz), 7.72 (d, 2H, Ar-H *J* = 8Hz), 8.31 (s, 1H, azomethine proton), 9.64 (s, 1H, NH, exchange with D_2O), 10.07 (s, 1H, OH, exchange with D_2O), 10.70 (s, 1H, CONH, exchange with D_2O). MS (m/z): 410 (M^+ + 1).

N'-(4-Chlorobenzylidene)-4-(tosylamino) benzohydrazide (2d)

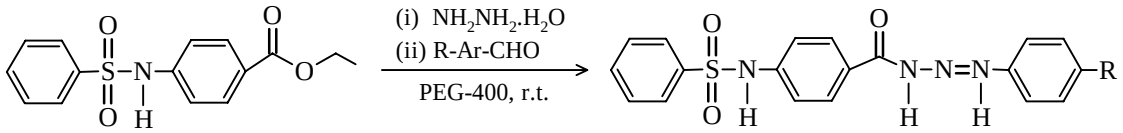
Yield 91%, m.p. 272-274^{o}C, IR (KBr, cm-^{1}): 3190, 1642, 1602, 1549, 1335 and 1158. ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.32 (s, 3H, CH_3), 7.01 (d, 2H, Ar-H *J* = 8Hz), 7.37 (d, 2H, Ar-H *J* = 8Hz), 7.69 (d, 2H, Ar-H *J* = 8Hz), 7.72 (d, 2H, Ar-H *J* = 8Hz), 7.74 (d, 2H, Ar-H *J* = 8Hz), 7.80 (d, 2H, Ar-H *J* = 8Hz), 8.24 (s, 1H, azomethine proton), 9.93 (s, 1H, NH, exchange with D_2O), 10.83 (s, 1H, CONH, exchange with D_2O). MS (m/z): 428 (M^+ + 1), 430 (M + 2).

N'-(4-(Dimethylamino)benzylidene)-4-(tosylamino) benzohydrazide (2h)

Yield 88%, m.p. 246-247^{o}C, IR (KBr, cm-^{1}): 3225, 1646, 1605, 1551, 1335 and 1158. ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.32 (s, 3H, CH_3), 2.91 (s, 6H, $2CH_3$), 6.98 (d, 2H, Ar-H *J* = 8Hz), 7.01 (d, 2H, Ar-H *J* = 8Hz), 7.37 (d, 2H, Ar-H *J* = 8Hz), 7.54 (d, 2H, Ar-H *J* = 8Hz), 7.69 (d, 2H, Ar-H *J* = 8Hz), 7.72 (d, 2H, Ar-H *J* = 8Hz), 8.21 (s, 1H, azomethine proton), 9.92 (s, 1H, NH, exchange with D_2O), 10.81 (s, 1H, CONH, exchange with D_2O). MS (m/z): 437 (M^+ + 1).

RESULTS AND DISCUSSION

The key intermediate 4-(toluene-4-sulfonylamino)-benzoic acid ethyl ester (**1**) was synthesized using following literature[24,25] procedure. Compound (**2**) was prepared by the reaction of compound (**1**) with hydrazine hydrate and aromatic aldehyde using PEG-400 as medium at room temperature in one pot. Using this method, we obtained excellent yields of the schiff bases having sulphonamido pharmacophore. The reaction sequence is outlined in Scheme 1.



1 **2a-h**

Scheme 1

Table 1: Physical data of Schiff bases (2a-h)

Product	R	Yield[a] (%)	M.P. (°C)
2a	OCH_3	92	223-224*
2b	OH	92	259-261
2c	$OCOCH_3$	88	233-234
2d	Cl	91	272-274*
2e	F	90	282-284
2f	Br	91	277-278
2g	H	91	248-250*
2h	$N(CH_3)_2$	88	246-247*

[a]Isolated yields based on ester.

[b]MPs and structures were confirmed by comparison of the IR, ^{1}H NMR mass analyses with those authentic materials. MPs of the compounds are in good agreements (11b).

Characteristic absorption of (**2a**) as one of the representative products (**2a-h**) has been presented bellow MS (m/z): 424 (M^+ + 1). IR (KBr, cm^{-1}): 3240 (NH, str.), 1640 (CONH, str.), 1606 (C = C, str.), 1549 (C = N, str.), 1335 and 1160 (SO_2, str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.32 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 7.01 (d, 2H, Ar-H *J* = 8Hz), 7.19 (d, 2H, Ar-H *J* = 8Hz), 7.37 (d, 2H, Ar-H *J* = 8Hz), 7.64 (d, 2H, Ar-H *J* = 8Hz), 7.69 (d, 2H, Ar-H *J* = 8Hz), 7.72 (d, 2H, Ar-H *J* = 8Hz), 8.32 (s, 1H, azomethine proton), 10.63 (s, 1H, NH, exchange with D_2O), 11.53 (s, 1H, CONH, exchange with D_2O).

The deployment of PEG eliminates the use of volatile solvents, catalyst, dehydrating agents, Dean-Stark apparatus and provides high yielding eco-friendly route. The formation of schiff bases occurs at room temperature in PEG-400 as greener medium. The *in situ* formed acid hydrazied did not require isolation, which save the time and improved the productivity. PEG is possibly to activate these compounds through hydrogen bonding. The PEG was recovered from the reaction mixture and was reused without loss of activity.

Table 2: Recyclability data of PEG for product (2a-h)

Product	PEG[a] cycle	Yield[b] (%)
2a	0	93
2b	1	85
2c	0	93
2d	1	92
2e	0	93
2f	1	92
2g	0	93
2h	1	92

[a] 0 Fresh PEG used for conversion and 1 recovered PEG used for conversion.

[b] % of recovered PEG after isolation.

CONCLUSION

In conclusion, we have developed a simple and efficient method for synthesis of schiff bases having sulphonamido pharmacophore using PEG at room temperature in one pot. The mildness, catalyst free and eco-friendly nature of the conversion, shorter reaction times and yields are excellent.

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