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An efficient and recyclable catalyst for synthesis of 1,3-diphenyl-3-(phenyl thio) propan-1-one derivatives and their antibacterial evaluation

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Abstract: A series of 1,3-diphenyl-3-(phenyl thio)propan-1-one derivatives were synthesized by reacting chalcone with thiophenol using 1-hexyl 3-methyl imidazolium acetate {[hmim]OAc} ionic liquid as a catalyst. These compounds are evaluated for their antibacterial activity & the ionic liquid used was recovered and reused four times without significant loss in its activity.

Keywords: C-S bond formation, Michael addition, ionic liquid, antibacterial activity, thiophenol

Introduction:

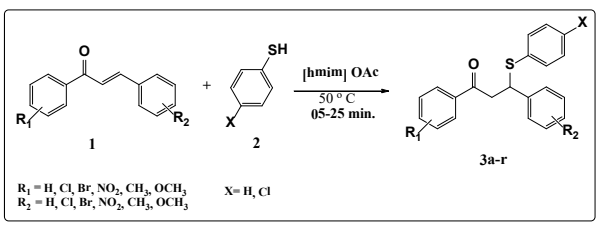
The Michael addition is one of the most proficient and atom-economical methodologies for carbon-carbon and carbon-heteroatom bond formation reaction, that includes the carbon-Michael reactions, [1-2] oxa-Michael reactions, [3-5] aza-Michael reactions, [6-9] and the thiol-Michael reactions [10-12] all of these have been studied over the years in organic synthesis, polymer chemistry and in materials science [13]

Thia-Michael addition reaction is one of the most crucial C-S bond-forming reactions in the synthesis of 1,3-diphenyl-3-(phenyl thio) propan-1-one derivatives that have valuable synthetic scaffolds for medicinal and synthetic organic chemists [14]. Sulfur-containing compounds are known to exhibit various biological activities, such as antibacterial [15], antimicrobial [16], antifungal [17], anticancer [18], anti-thrombotic, antioxidant and anti-diabetic effects [19]. Moreover the thia-Michael addition to α,β-unsaturated carbonyl compounds provides a practical strategy for the selective protection of C=C bond of conjugated enones, because regeneration of the double bond can be accomplished easily by elimination of the sulfur moiety. [20, 21]

Ionic liquids are salts composed of organic cations and organic or inorganic anions. Ionic

liquids have gained significant awareness as an environmentally benign reaction medium in organic synthesis because of their exceptional properties of non-flammability, non-volatility, recyclability and its ability to dissolve a wide range of materials [22]. Though primarily used as solvents, they are now finding applications in various fields like catalysis; Ionic liquids are capable to restrict many of the negative effects of the conventional organic solvents or other catalysts during catalytic reactions. Therefore compared to conventional organic solvents, the use of ionic liquids for synthesis and catalysis has a number of advantages. [23]

Conventional methodologies to achieve 1,4-addition of mercaptans either involves activation of acceptor olefin by acid or de-protonation of thiol by a base. Constant efforts have been made to develop newer and simpler methodologies for thia-Michael addition that have led to exploit variety of catalysts such as Lewis acid catalyst [24], base catalyst [25], silica supported catalyst [26], sodium metal [27], iodine [28], and ionic liquids i.e. [pmim]Br [29], L-proline nitrate [30], phosphonium chloride [31], $Yb(OTf)_3$ in $[bmim]BF_4$ [32], magnetic cobalt particles [33] etc.. Most of these approaches suffer from one or more drawbacks such as long reaction time, requirement of high temperature, low to moderate yields, use of metal catalyst which are highly expensive and no reuse of catalyst. To overcome these drawbacks herein we report the clean, simple and rapid $[hmim]OAc^-$ ionic liquid catalyzed thia-Michael addition reaction for preparation of 1,3-diphenyl-3-(phenyl thio) propan-1-one derivatives.(Scheme 1)



Scheme 1: Michael addition of thiophenol to chalcones catalyzed by [hmim]OAc ionic liquid

Experimental procedure:

General procedure of Michael addition of thiophenol to chalcone:

To a 50 mL round-bottom flask containing [hmim] OAc (4 mmol) ionic liquid were added chalcone **1** (3 mmol) and thiophenol **2** (3.3 mmol). The reaction mixture was stirred at 50°C for appropriate time (as shown in Table 1). Once the reaction was completed (monitored by TLC) some crushed ice was added to the reaction mixture. The solid formed was filtered and further purified by water washing to give the pure product. The aqueous layer was evaporated by distillation to remove water [34] and the residue catalyst was further reused 4 times (Graph 1).

Biological evaluation method

Disk diffusion assay.

The anti-tubercular potential of synthesized compounds was evaluated as per the previous reported method [35]. In brief, each dried paper disk (Whatmann filter paper No.1) contained each of the compound 30 µL (1 mg/ mL). Each disk was then placed on the surface of the sterile solidified Muller Hilton agar which was spread with inoculums of *P. aeruginosa* and *M. tuberculosis (Mtb).* Rifampicin was used as the standard (1 mg/mL). The plates were kept in refrigerator for diffusion for 40 min and then transferred to the incubator at 37ºC. The *P. aeruginosa* plates are incubated for 24 h while the *Mtb* plates were incubated for 5 days after incubation, the zones around the discs were measured by the zone scale (Himedia Pvt. Ltd. Mumbai).

Resazurin micro titer assay (REMA).

The REMA plate assay was carried out as described elsewhere [36]. Briefly, 100 µL of nutrient broth and Middlebrook7H9-S liquid (containing 0.1% casitone, and 0.5% glycerol and supplemented with oleic acid, albumin, dextrose, and catalase) both was dispensed in each well of a sterile flat-bottom 96-well plate, and serial two fold dilutions of each compound were prepared directly in the plate. One hundred microliters of inoculums was added to each well. The plate was covered, sealed in a plastic bag, and incubated at 37°C. After incubation (one day for *P. aeruginosa* and 7 days for *Mtb)*, 30 µL of resazurin solution (0.01% in sterile de-ionized water) was added to each well, and the plate was re-incubated overnight. A change in color from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in color. The concentrations used for this assay were compounds (3.90 µg/mL -500 µg/mL) and RIF (3.90 µg/mL -500 µg/mL)

Table 1: Preparation of 1, 3-diphenyl-3-(phenylthio)propan-1-one derivatives catalyzed by {[hmim]OAc} ionic liquid

Entry	R_1	R_2	X	Time (min.)	Yield [a, b] (%)
3a	H	H	H	10	95
3b	H	H	Cl	05	97
3c	4-Cl	4-Br	H	10	95
3d	H	4-NO_2	Cl	11	96
3e	H	2,4-Cl	H	07	95
3f	H	2,4-Cl	Cl	10	95
3g	4-NO_2	H	H	25	90
3h	H	3-NO_2	Cl	20	97
3i	H	4-OCH_3	H	22	93
3j	4-OCH_3	4-OCH_3	H	24	95
3k	4-Cl	4-Cl	H	20	95
3l	H	4-Cl	Cl	20	96
3m	4-Br	4-CH_3	H	20	95
3n	4-Br	H	H	15	98
3o	4-OCH_3	3-NO_2	H	11	94
3p	H	4-Cl	H	22	96
3q	H	4-OCH_3	Cl	15	92
3r	3-CH_3	H	H	13	90

Reaction condition: Chalcone (3 mmol), thiophenol (3.3 mmol) and [hmim]OAc (4 mmol) at 50°C. [a] isolated yield; [b] all the products were characterized by IR spectra and some of them were analysis by ^{1}H NMR, ^{13}C-NMR and MS spectral data.)

Spectral data:

1, 3-Diphenyl-3-(phenylthio)propan-1-one : (Table 1, entry a) Mp. : 114-115°C ; **IR:** 3060, 2903, 1677, 1477, 1451, 1334, 1229, 1167, 1078, 981, 734, 695 cm^{-1}; ^{1}H **NMR ($CDCl_3$): δ** 3.63 (dd, 2H), 4.96 (t, 1H), 7.18-7.56 (m, 13H), 7.89 (d, 2H); **^{13}C NMR:δ** 191.2, 134.9, 131.1, 128.8(2C), 128.2, 127.6, 127.1, 123.2 (2C), 123.0 (2C), 122.8 (2C), 122.4 (2C), 122.1 (2C), 121.8, 43.2, 39.2 MS: *m/z*318.10

3-(4-Chlorophenylthio)1,3-diphenylpropan-1-one: (Table 1, entry b) Mp: 105-106°C; IR: 3063, 3029, 2893, 1675, 1447, 1336, 1228, 1179, 1094, 1077, 981, 816, 748, 699, 688cm^{-1}; ^{1}H **NMR ($CDCl_3$): δ** 3.55 (dd, 1H) 3.65 (dd, 1H) 4.85 (t, 1H) 7.15-7.65 (m, 12H) 7.85(d, 2H); **^{13}C NMR :δ** 191.5, 135.7, 131.4, 129.0 (2C), 128.5, 128.1, 127.3, 123.7 (2C), 123.4 (2C), 123.2(2C), 122.8 (2C), 122.5 (2C), 122.2, 43.27, 39.2; MS: m/z 351.2.

3-(2,4-Dichlorophenyl)-1-phenyl-3-

(phenylthio)propan-1-one: (Table 1, entry e) Mp. : 108-109°C; IR: 3068, 2917, 1684, 1577, 1470, 1323, 1219, 1068, 823, 735, 688, 622 cm^{-1}; ^1H **NMR ($CDCl_3$): δ** 3.47 (dd, 1H), 3.62 (dd, 1H), 5.35(t, 1H), 7.13-7.40 (m, 8H), 7.48(1H), 7.55(2H), 7.88 (d, 2H).**^{13}C NMR:δ** 191.0, 132.1, 131.8, 131.1, 129.3, 128.1, 128.0 (2C), 124.3, 124.1, 123.8(2C), 123.4(2C), 122.8 (2C), 122.2(2C), 121.9, 38.9, 38.6. MS: m/z 386.03

1-(4-Bromophenyl)-3-(phenylthio)-3-p-tolylpropan-1-one: (Table 1, entry m) Mp: 94-95°C; IR: 2917, 1683, 1584, 1471, 1328, 1220, 1177, 1066, 984, 809, 734, 692 cm^{-1}; ^1H **NMR ($CDCl_3$): δ** 2.28 (s, 3H), 3.54 (dt, 2H), 4.90 (t, 1H), 6.99 (d, 2H), 7.06 (d, 2H), 7.22 (dt, 1H) 7.34 (m, 4H), 7.55 (d, 2H) 7.72 (d, 2H); **^{13}C NMR:δ** 190.9, 132.6, 131.9, 130.2, 129.1, 127.3 (2C), 126.6 (2C), 124.3 (2C), 123.9 (2C), 123.6 (2C), 123.2, 122.3 (2C), 122.2, 42.7, 39.5, 15.8; MS: m/z 410

1-(4-Bromophenyl)-3-phenyl-3-(phenylthio) propan-1-one:(Table 1, entry n) Mp.:114-115°C **IR:**3065, 3022, 2021, 1685, 1578, 1223cm^{-1}; ^1H **NMR ($CDCl_3$): δ :**7.67 (dd, 2H), 7.45-7.53 (m, 2H), 7.10-7.21 (m, 10H), 4.40-4.47 (m, 1H), 3.55-3.62 (m, 2H); **^{13}C NMR:δ**192.1, 138.2, 134.1, 133.9, 133.5, 132.7, 131.6, 129.3, 128.7, 127.5, 127.4, 127.3, 46.3, 43.8; MS: m/z 397 (M+1)

Result and discussion:

Initially, the Michael addition reaction of thiophenol (3.3 mmol) to chalcone (3 mmol) was selected as a model reaction to set up the most favorable reaction conditions. Traditional organic solvents such as DMF, acetone, toluene, acetonitrile, chloroform and dichloromethane were used as reaction medium for the model reaction in the absence of any catalyst at room temperature. The adduct yields were unsatisfactory (trace to 32%) even after 1 h of reaction (entries 1–6, **Table 2**).

Table 2: Influence of reaction solvents on the Michael addition reaction between thiophenol and chalcone without any catalyst [a]

Entry	Solvent	Time (min.)	Yield [b] (%)
1	DMF	60	24
2	Acetone	60	19
3	Toluene	60	22
4	Dichloromethane	60	Trace
5	Chloroform	60	Trace
6	Acetonitrile	60	32
7	[hmim] Cl	40	68
8	[hmim] Br	30	70
9	[hmim] OAc	10	95

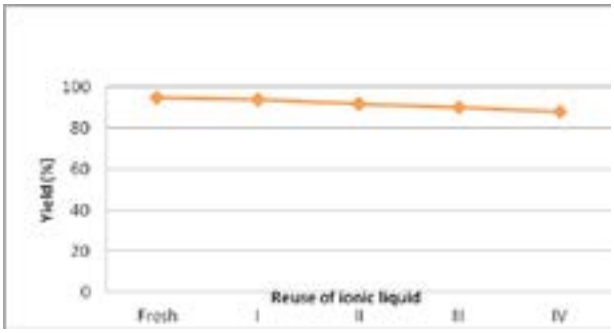
[a] Reaction conditions: chalcone (3 mmol) and thiophenol (3.3 mmol) [b] Isolated yield

Once the study of organic solvents was completed, ionic liquid was exploited as catalyst, and as an alternative to the volatile organic solvent for model reaction and we observed that ionic liquid was worked as an efficient catalyst for the reaction between thiophenol and chalcone to form 1, 3-diphenyl-3-(phenylthio) propan-1-one, which elucidate the dual role of ionic liquid as reaction media as well as catalyst. The elucidation of high reactivity of thiophenol in {[hmim]OAc} ionic liquid might be due to the higher dissociation constant of thiophenol in ionic liquid compare to organic solvents.[37]

Structural determination of isolated compound of model reaction:

The product was characterized by FT-IR spectra. The formation of product was indicated by characteristic peak shift of carbonyl group in infrared spectrum (IR) from 1650 to 1677 cm^{-1} due to the disappearance of conjugation of carbonyl group with double bond. The determination of structure for the product was

further confirmed by ^{1}H NMR spectra. In NMR spectrum, α, and β−protons disappeared and two new peaks appeared at 4.96 (t, 1H) and 3.63 (dd, 2H) for Ar-S-CH- and $ArCOCH_2$- protons, respectively confirmed the Michael addition reaction of thiophenol to chalcone. The ionic liquid used for model reaction was recovered and reused four times successfully without significant loss in the activity.



Graph 1: Reuse of ionic liquid for the given model reaction

In order to find out the scope of this method, we prepared several derivatives of 1,3-diphenyl-3-(phenylthio)propan-1-one using {[hmim]OAc} ionic liquid as shown in **Table 1**

Biology results:

Table: 3 Antibacterial activities of synthesized compounds

Bacteria	Compound code	Disk diffusion Zone of inhibition (mm)	MIC Concentration µg/mL
P. aeruginosa	HSM5 / 3a	12	250
	HSM 7 / 3 c	08	>500
	JSM 08 / 3h	13	125
	HSM 13 / 3e	18	15.6
M. tuberculosis	HSM5 / 3a	12	250
	HSM 7 / 3c	06	>500
	JSM 08 /3h	11	125
	HSM 13 / 3e	16	62.5
Rifampicin	RIF	21	3.9

The results are the mean values of three independent experiments.

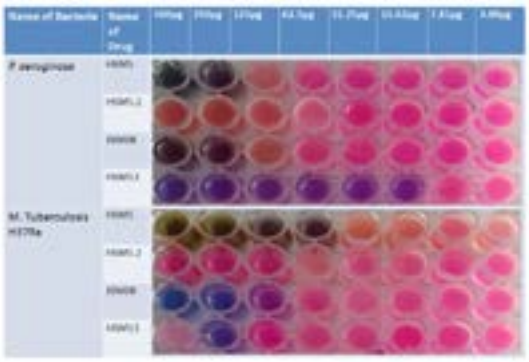


Figure 1: The results obtained in the Resazurin Microtiter Plate Assay.

The results of antimicrobial potential of synthesized compounds by disk diffusion assay (Table 3) showed that compound HSM 13/3e showed highest zone of inhibition 18 mm as compared to RIF 21 mm.

The MIC calculated by REMA assay showed that the compound HSM 13/3e showed potent inhibitory activity towards *P. aeruginosa* and *M. tuberculosis*. The MIC values of HSM 13/3e towards *P. aeruginosa* 15.6 µg/mL and *M. tuberculosis* 62.5 µg/mL which is considered to be good as compared to standard RIF 3.9 µg/mL (Figure 1).

Conclusion:

In conclusion, we developed an eco-friendly, an efficient and rapid synthesis of 1,3-diphenyl-3-(phenyl thio)propan-1-one derivatives catalyzed by {[hmim]OAc} ionic liquid. The simple work up method, avoidance of toxic volatile organic solvents, reuse and recycling of ionic liquid and good to excellent yields of the products are the silent features of this developed method.

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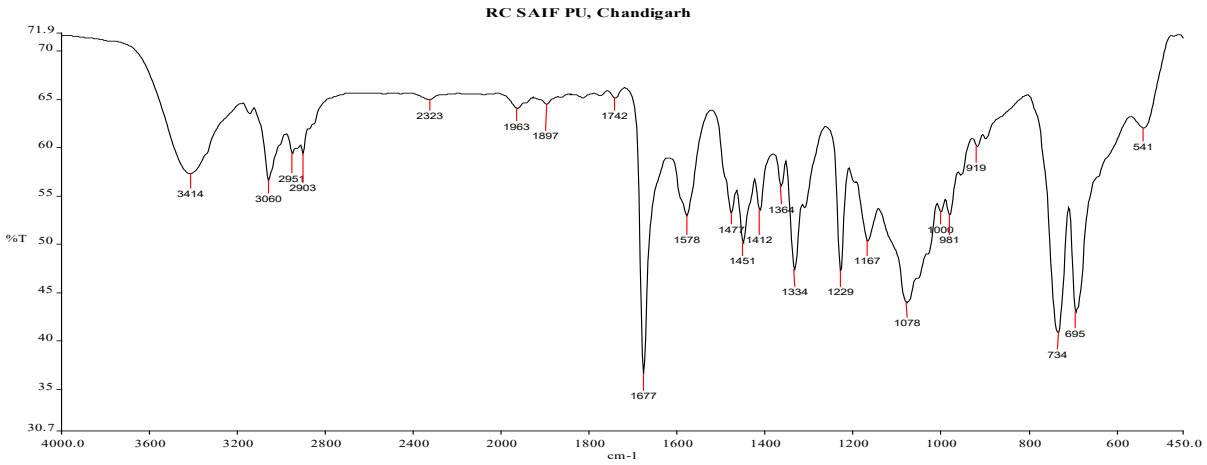
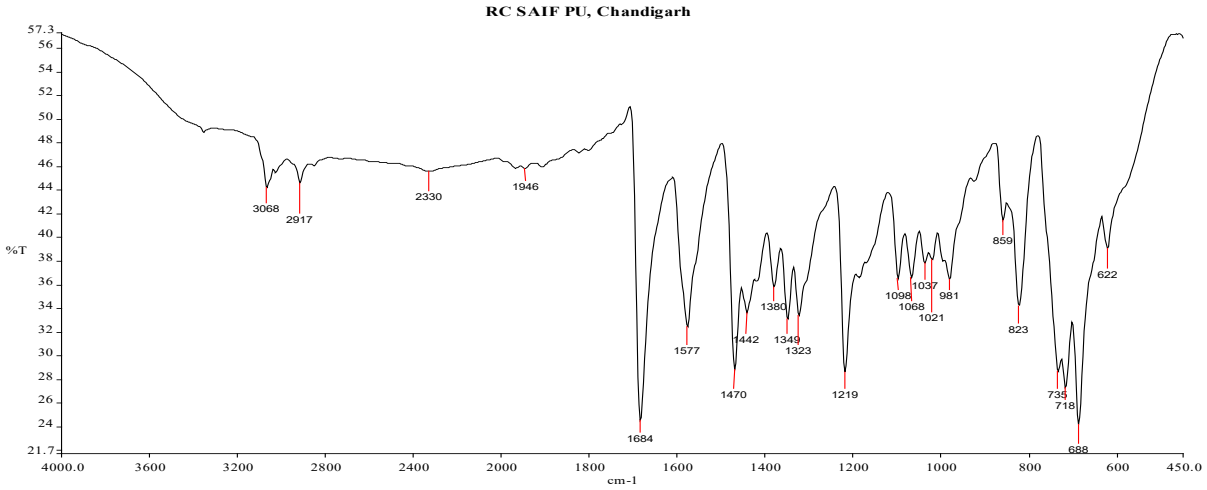
Supplementary data:



Spectrum Name: Shreyas-11.sp Description: HSM-05

Date Created: fri dec 14 16:43:46 2012 India Standard Time (GMT+5:30)

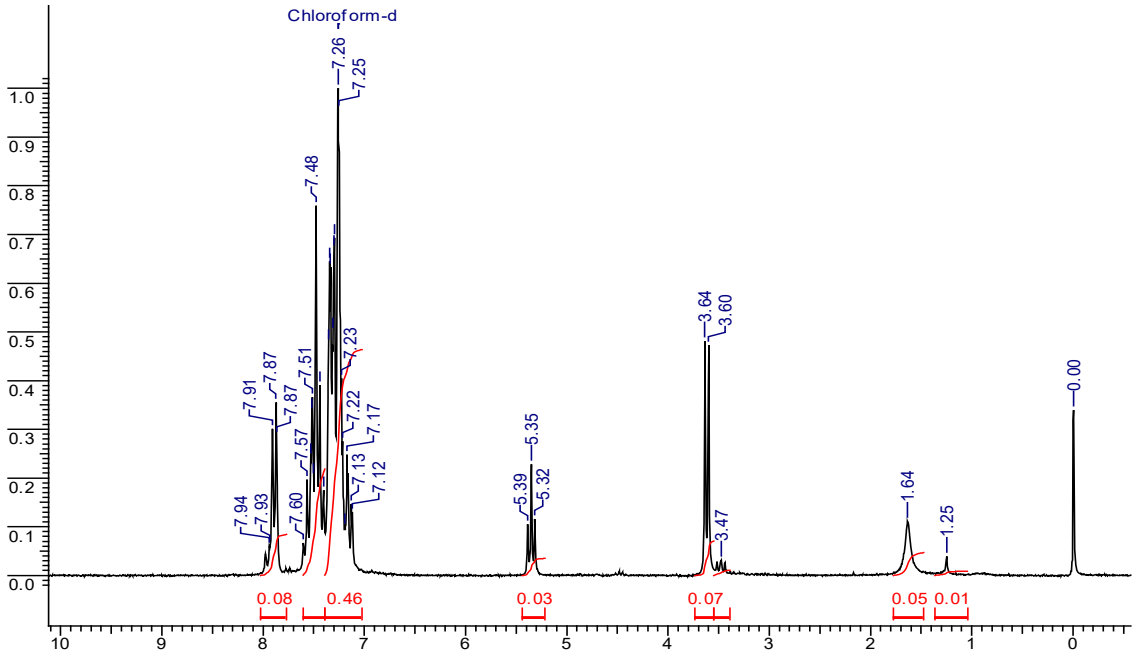
I.R. spectrum of 1, 3-diphenyl-3-(phenylthio)propan-1-one (Table 1, entry a)



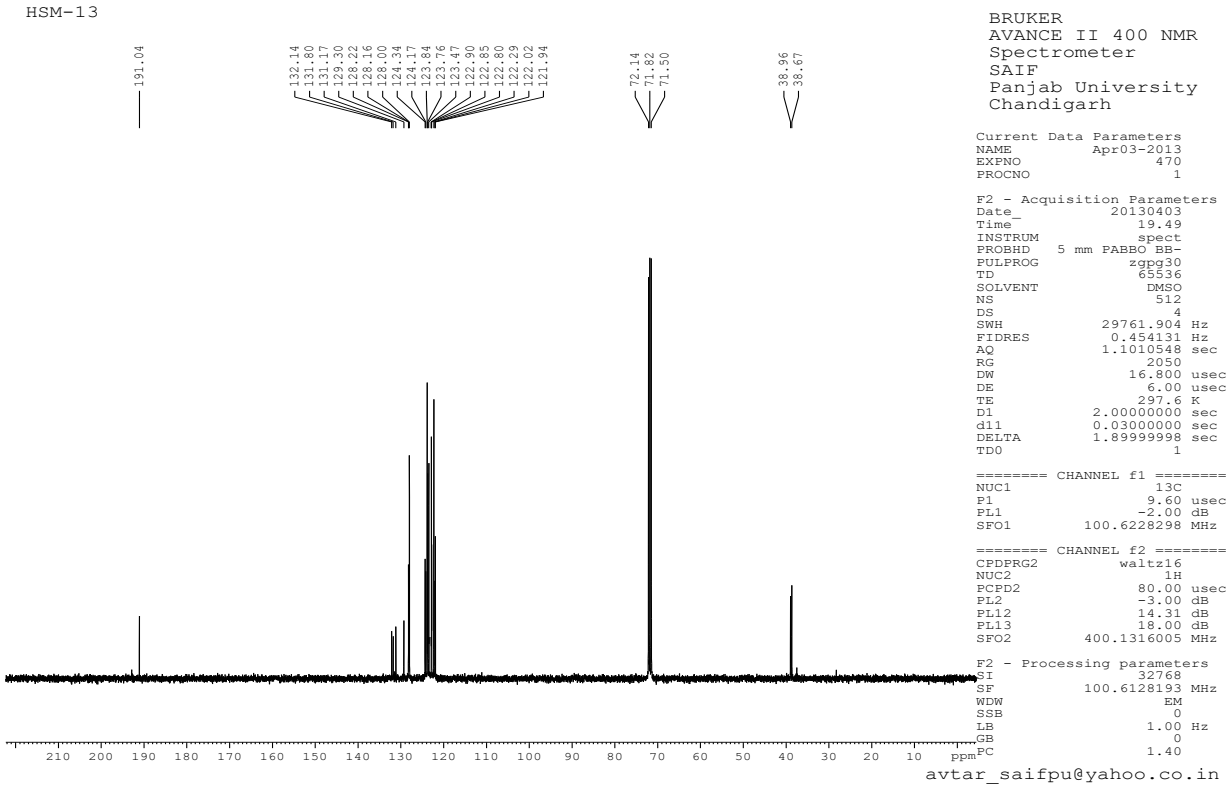
Spectrum Name: Shreyas-15.sp Description: HSM-13

Date Created: fri dec 14 16:48:12 2012 India Standard Time (GMT+5:30)

I.R. spectrum of 3-(2,4-dichlorophenyl)-1-phenyl-3-(phenylthio)propan-1-one: (Table 1, entry e)



^{1}H NMR spectrum of 3-(2,4-dichlorophenyl)-1-phenyl-3-(phenylthio)propan-1-one: (Table 1, entry e)



^{13}C NMR spectrum of 3-(2,4-Dichlorophenyl)-1-phenyl-3- (phenylthio)propan-1-one: (Table 1, entry e)

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