

J. Surface Sci. Technol., Vol 28, No. 3-4, pp. 111-131, 2012
© 2012 Indian Society for Surface Science and Technology, India.

Micelle Catalyzed Monosulfonylation of Amines and Amino Acids in Aqueous Media

BALU PAWAR and SUNIL BHAGWAT*

Chemical Engineering Department, Institute of Chemical Technology, Matunga, Mumbai-400019, India.

Abstract — An efficient synthetic route was developed for the formation of monosulfonylated products in aqueous organized media at room temperature (303 ± 1 K) in the presence of a surfactant (viz. CTAB) as catalyst. The method is operationally simple and more effective as compared to the methods reported in terms of the product yield as well as kinetics. CTAB and CPB catalyze the sulfonamide synthesis better than SDS and Triton X-100.

Keywords : *Sulfonamide synthesis, Monosulfonylation, Micellar catalysis, Amino compounds, Sulfonyl chloride.*

INTRODUCTION

Reactions conducted in aqueous media have attracted interest because of unique reactivity which is not attained in an organic solvent. Water is considered as an ideal low cost solvent due to environmental concerns [1–2]. Aqueous micellar solutions can alter the kinetics [3–4], yield [5] as well as the selectivity [6–9] of many organic reactions to a higher extent compared to organic solvents. Substrates attain a suitable orientation in a micelle due to the dual nature of micelles. The hydrophobic core of micelles solubilizes sparingly soluble substrates, intermediates and products in water [10–12]. Sulfonamides are used as antibacterial, anticancer, anticonvulsant, anti-inflammatory, antitumor, antiviral agents and also as HIV protease inhibitors [13–14]. Important examples are amprenavir, celecoxib, sildenafil and sumatriptan [15]. Considerable efforts have been directed towards the development of novel sulfonamides through the reaction of amino compounds and sulfonyl chlorides. However, in the

*Corresponding Author. E-mail : ss.bhagwat@ictmumbai.edu.in. Tel : +91-22-33612011, Fax : +91-22-33611020

case of less reactive amines, this procedure requires base catalysis, high temperatures and organic solvents [16]. In the case of primary amines with an electron withdrawing group, bis-sulfonylation occurs as a side reaction and necessitates a subsequent monodesulfonylation step in the presence of tetrabutylammonium fluoride (TBAF) [17]. The hydrolysis of sulfonyl chloride is also a major hindrance in the conventional synthesis of sulfonamide under basic conditions [18–21].

Recently, Diang and Mani [22] have developed a green technique for the synthesis of sulfonamides in water. The major hurdle of low isolated yield of sulfonamide was eliminated by addition of tetrabutylammonium bromide (TBAB) as a catalyst. Sulfonylation of amines and amino acids in the presence of β -cyclodextrin as a catalyst increases the reaction rate as well as the isolated yield of sulfonamides [23]. The catalytic effect of surfactants on a variety of organic reactions is well known in literature [24–25]. The solubilization of amino compounds, sulfonyl chloride and product sulfonamides inside the micelles results in a high concentration of reagents within a confined region and influences the reaction mechanism, kinetics and yield. Micellar solutions can provide a conducive environment for the desired reaction without the addition of any organic solvent.

The objective of the present work is to study the effect of micellar catalysis on monosulfonylation of amines and amino acids (Fig. 1). Generally, the separation

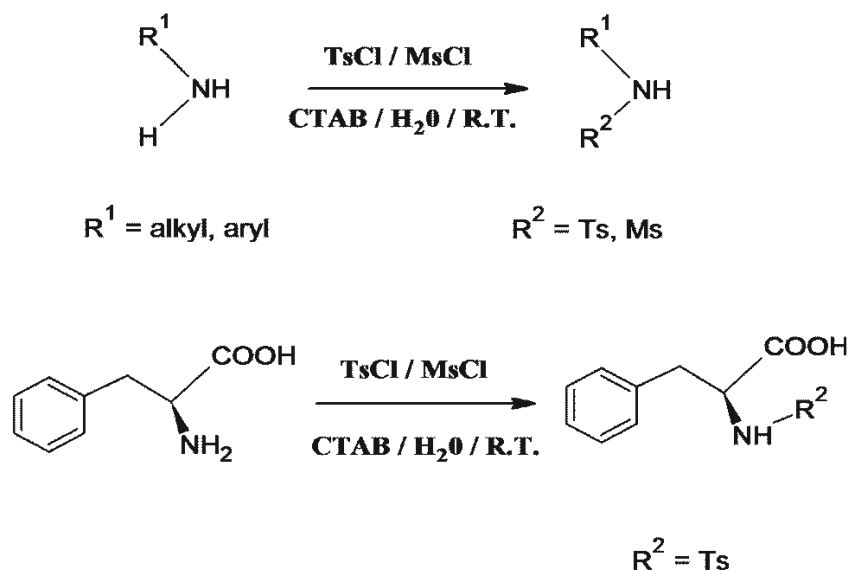


Fig. 1. Sulfonylation of amines and amino acid in CTAB-H₂O micelle.

of the product from surfactant solution requires a special separation step. The use of expensive solvents and amine bases is eliminated in the present work since the product sulfonamides are easily isolated by simple filtration of the precipitated solid.

EXPERIMENTAL

Materials and Methods :

Sodium dodecyl sulfate (SDS) was procured from M/s Sisco Research Laboratories Pvt. Ltd. India, cetylpyridinium bromide (CPB) was obtained from M/s Aldrich Chemical Company Inc. U.S.A., triton X-100, cetyltrimethylammoniumbromide (CTAB), *p*-toluene sulfonyl chloride (TsCl), methane sulfonyl chloride (MsCl), triethyl amine (TEA), various amines, ethanol amine and L (-) phenyl alanine were procured from M/s SD-Fine Chemicals Pvt. Ltd. India. All these chemicals were of analytical grade and were used without further purification.

General procedure employed for the synthesis of N-sulfonylated amino compounds :

A 0.025 dm³ solution of surfactant (different concentrations) and amine (0.025 mol.dm⁻³) was added to a 0.1 dm³ glass reactor equipped with a six bladed turbine agitator (0.05 m diameter). The speed of agitation was maintained at 600 rpm and the reaction was carried out at 303 ± 1 K. The TsCl or MsCl (0.03 mol.dm⁻³) was added after agitating the reaction mixture for five minutes, while TEA (0.03 mol.dm⁻³) was added additionally when conducting the reaction with L (-) phenyl alanine. The reaction was monitored by thin layer chromatography (TLC). The product was separated by simple filtration followed by washing with water. In those cases where the product was liquid, the reaction mixture was extracted with ethyl acetate. The progress of reaction was monitored by thin layer chromatography (TLC) and Gas chromatography (GC). The product was extracted by diethyl ether (3*0.01 dm³) after the reaction was completed. The organic layer was separated and analyzed using gas chromatography (Chemito 8610 equipped with an OV-17 packed column and flame ionization detector). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a crude product which was further purified by column chromatography (hexane : ethyl acetate; 8 : 2). The products were characterized by fourier transform infrared spectroscopy (FT-IR) using a Perkin-Elmer spectrum 100, mass spectrometry (MS) on Finnigan LCQ Advantage Max with electrospray ionization spectroscopy (ESI, positive mode) and nuclear magnetic resonance (NMR) by Bruker Avance 400 MHz spectrometer. All the NMR spectra were recorded using deuterated chloroform (CDCl₃) or dimethyl sulfoxide (DMSO) as solvent with tetra methyl silane (TMS) as an internal standard.

***N*-Tosyl morpholine (11) :**

¹H-NMR (400 MHz, TMS, CDCl₃) δ ppm : 2.41 (s, 3 H, Me), 2.81 (t, 4 H, 2*NCH₂), 3.60 (t, 4 H, 2*OCH₂), 7.44–7.47 (d, 2 H, *J* = 8.3 Hz, Ar-H), 7.6–7.62 (d, 2 H, *J* = 8.3 Hz, Ar-H).

FT-IR (KBr) cm⁻¹ : 2927, 1595, 1161, 812.

ESI-MS (m/z) : 242 (M+1).

***N*-Tosyl antipyrine (17) :**

¹H-NMR (400 MHz, TMS, CDCl₃) δ ppm : 2.12 (s, 3 H, Me), 3.00 (s, 3 H, Me), 3.25 (s, 3 H, Me), 7.18–7.40 (m, 5 H, Ar-H), 7.64–7.80 (m, 4 H, Ar-H).

FT-IR (KBr) cm⁻¹ : 3443, 2821, 1628, 1595, 1312, 1153, 933, 820.

ESI-MS (m/z) : 358 (M+1).

***N*-(*p*-Toluenesulfonyl)-L-phenylalanine (23) :**

¹H-NMR (400 MHz, TMS, CDCl₃) δ ppm : 2.33 (s, 3 H, Me), 2.70 (dd, 1 H, *J* = 8.80, 13.2 Hz, CH₂), 2.90 (dd, 1 H, *J* = 5.2, 13.4 Hz, CH₂), 3.8–3.87 (m, 1 H, CH), 7.08–7.23 (m, 7 H, Ar-H), 7.42 (d, 1 H, *J* = 8.80 Hz, Ar-H), 7.45 (d, 1 H, *J* = 8.80, Ar-H), 12.69 (br, 1H, COOH).

FT-IR (KBr) cm⁻¹ : 3319, 2924, 1711, 1596, 1330, 1157, 932, 820.

ESI-MS (m/z) : 320 (M+1).

RESULTS AND DISCUSSION

Various parameters which affect the reaction under investigation such as surfactant type, concentration and type of amino compound were studied :

Solubility of aniline :

Solubility is one of the important factor for enhancing the rate of the reaction due to solubilization of substrates in micellar core. The solubility of aniline increases linearly with the concentration of CTAB and the rise is less pronounced below the CMC of CTAB as shown in Fig. 3. This suggests that the increase in solubility is due to the formation of micelles. Also, the solubilization of aniline was studied in micellar solution of SDS and TX-100, the solubility of aniline increases linearly with its concentration as shown in Table 1.

Effect of surfactant type :

The effect of various types of surfactant on the formation of sulfonamide of aniline with TsCl was studied in water at 303±1 K. It was found that the rate of reaction

TABLE 1.

Solubility of aniline in different surfactant solution

Entry	Surfactant	Solubility (mol.dm ⁻³)
1	-	0.28
2	CTAB	0.67
3	SDS	0.45
4	TX-100	0.52

was highly dependent on the nature of surfactant used. When the reaction was carried out in water in the absence of any surfactant, the rate of the reaction was low because of poor solubility of aniline in water (Entry 1, Table 2). Fig. 2 shows the conversion of aniline in water as a function of time. The rate of the reaction fits to a second

TABLE 2.Effect of different surfactants on *N*-tosylation of aniline with TsCl in 20 min^a.

Entry	Surfactant	Concentration (mol.dm ⁻³)	Isolated Yield (%)
1	None	-	65
2	SDS	0.05	80
3	TX-100	0.05	65
4	CPB	0.05	88
5	CTAB	0.025	85
6	CTAB	0.05	94
7	CTAB	0.07	93

^aInitial concentration of aniline : 0.025 mol.dm⁻³, initial concentration of TsCl : 0.030 mol.dm⁻³, Temperature : 303±1 K.

order rate equation with second order rate constant of 4.2 dm³.mol⁻¹.min⁻¹. The surfactant solutions were prepared well above the critical micelle concentration (CMC). Anionic surfactant SDS shows less efficiency with 80% isolated yield of product in 20 minutes (Entry 2, Table 2). Although with nonionic surfactant (Triton X-100), change in yield was insignificant (Entry 3, Table 2). However, the cationic surfactant CTAB gives 85–94% isolated yields of sulfonamide (Entries 5-7, Table 2) followed by CPB (Entry 4, Table 2). The selectivity towards the monosulfonylation product was 100%. No bis-sulfonylation of amino compounds was detected under the reaction

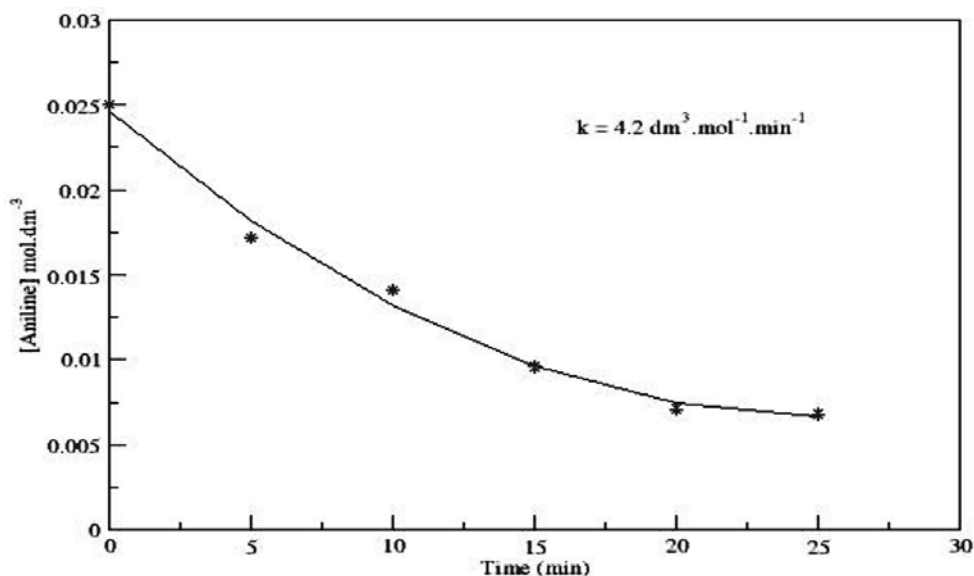


Fig. 2. Concentration-time curve for the reaction of aniline with TsCl in water in the absence of any surfactant. Initial concentration of aniline : $0.025 \text{ mol.dm}^{-3}$, initial concentration of TsCl : 0.03 mol.dm^{-3} , Temperature : $303 \pm 1 \text{ K}$.

conditions employed. CTAB was therefore chosen as the surfactant for studying the effect of other parameters. The rate of reaction was found to be higher in CTAB than TTAB and DTAB. The CMC of CTAB has lowest amongs these and this leads to a higher proportion of surfactant in micellar form compared to TTAB and DTAB at the same concentration. The CMC decreases with increasing chain length and hence the reaction is catalysed to a greater extent [25, 27].

Effect of surfactant concentration :

The effect of surfactant (CTAB) concentration on sulfonamide formation of aniline with TsCl was investigated. The concentration of CTAB was varied from $0.025 \text{ mol.dm}^{-3}$ to 0.07 mol.dm^{-3} which gave conversion of aniline to product sulfonamide between 85 to 94% (Entries 5-7, Table 2). Fig. 4 shows that, the rate of the reaction increases linearly with CTAB concentration upto 0.05 mol.dm^{-3} . A further increase in the CTAB concentration does not increase the rate further.

Kinetics :

In order to study the kinetics of reaction between aniline and TsCl, % conversion of aniline was studied as a function of time in water as well as CTAB surfactant solution (Table 3).

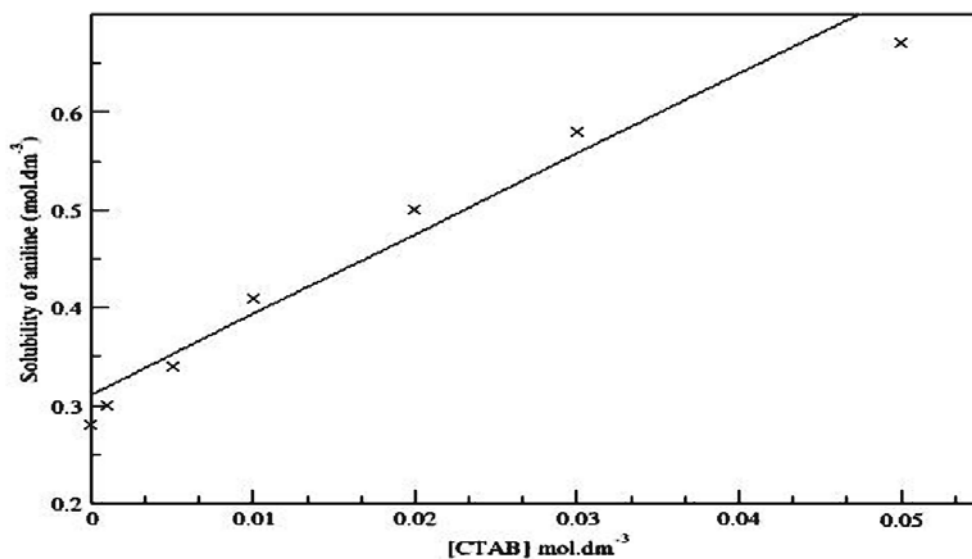


Fig. 3. Solubility of aniline in aqueous micellar solution of CTAB.

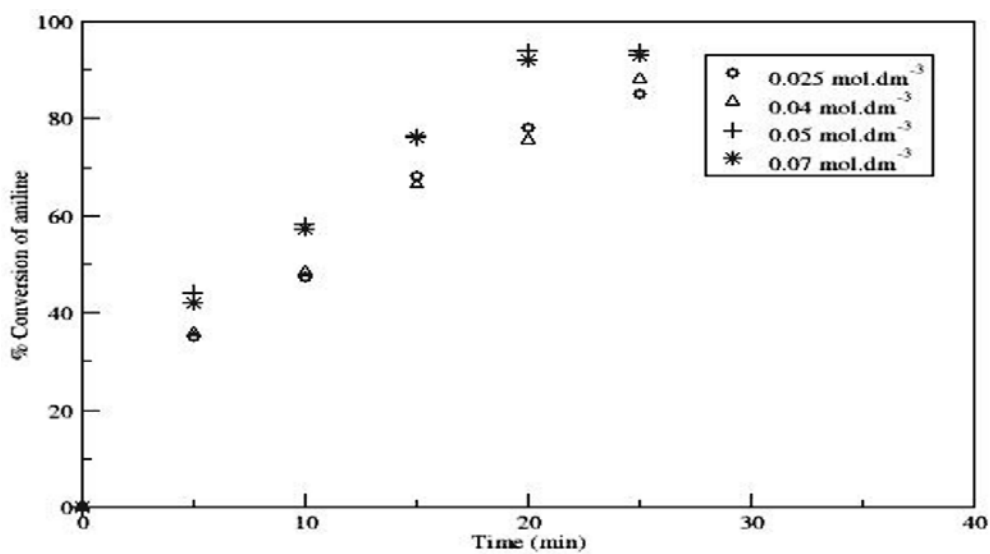


Fig. 4. Effect of surfactant (Cetyl trimethylammonium bromide) concentration. Initial concentration of aniline : $0.025 \text{ mol.dm}^{-3}$, Initial concentration of TsCl : 0.03 mol.dm^{-3} , Temperature : $303 \pm 1 \text{ K}$.

TABLE 3.% conversion of aniline as a function of time in water^a

Time (min)	% conversion of aniline ^b (Isolated Yield (%)) ^c	
	Without CTAB	With CTAB
0	0	0
5	31(29)	42(41)
10	44(40)	67(55)
20	68(65)	95(94)
40	72(88)	96(94)
60	75(71)	95(93)

^aInitial concentration of aniline : 0.025 mol.dm⁻³, initial concentration of TsCl : 0.030 mol.dm⁻³, Temperature : 303±1 K.

^b% conversion of reaction was calculated by gas chromatography.

^cIsolated yield(%)

The concentration-time data for the reaction at CTAB concentration between 0.025 mol. dm⁻³ to 0.07 mol.dm⁻³ was fitted to a second order rate equation-(1). All the other conditions such as reactant concentration and the temperature were maintained at the same level in all the experiments. The second order rate constant (k), was evaluated using equation-(1),

Let the reaction be expressed as,



Where, A and B are the reactants and P is the product

$$-r_A = kC_A \cdot C_B = -\frac{dc_A}{dt} = kC_{A0}^2(1 - X_A)(M - X_A) \quad (1)$$

Where, $M = C_{B0}/C_{A0}$, is the initial molar ratio of TsCl to aniline, C_A is the concentration of aniline, C_B is the concentration of TsCl and k is the second order rate constant, C_{A0} is the initial concentration of aniline and X_A is the conversion of aniline.

Integrated form of this equation is given by equation-(2),

$$\ln \left[\frac{(M-X_A)}{M(1-X_A)} \right] = C_{A0}kt (M - 1) \quad (2)$$

The rate constant k was obtained from the slope of $\ln \left[\frac{(M-X_A)}{M(1-X_A)} \right]$ against time 't'.

The linearity of this plot confirms the second order behavior of the reaction. The increase in the concentration of CTAB beyond 0.05 mol.dm^{-3} , resulted in a negligible improvement in the kinetics as shown in Fig. 5. Micelles cause an increase in the local concentration of substrates and hence this reaction takes place more easily in micellar solutions [28]. The molecular environment of the reagents is thus different in the presence of surfactant solutions. Aniline is solubilized in the aqueous micellar solution and attains a preferred molecular orientation and this influence the reaction rates and selectivity [29].

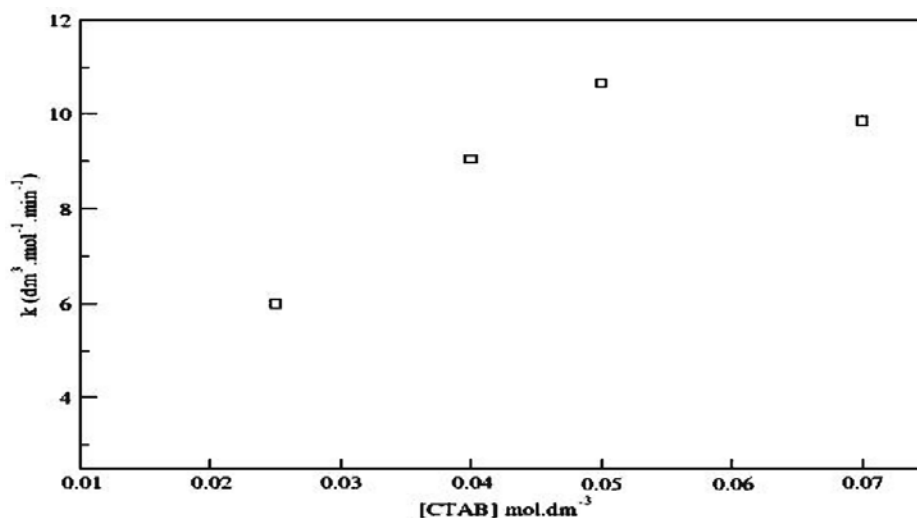
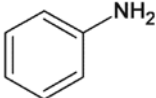
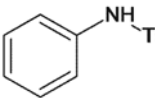
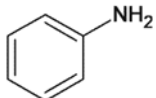
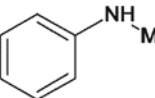
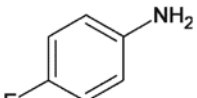
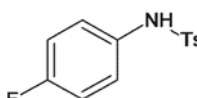
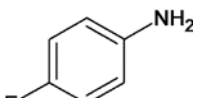
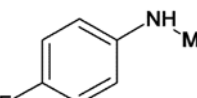
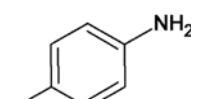
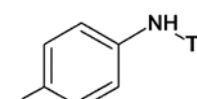
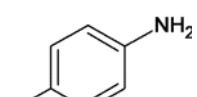
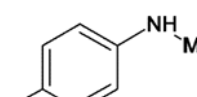
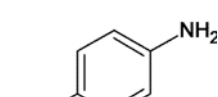
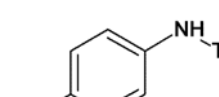
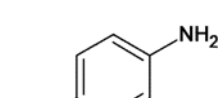
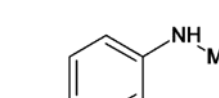


Fig. 5. Second order rate constant (k) of reaction in the presence of CTAB at different concentrations. Initial concentration of aniline : $0.025 \text{ mol.dm}^{-3}$, initial concentration of TsCl : $0.030 \text{ mol.dm}^{-3}$, Temperature : $303 \pm 1 \text{ K}$.

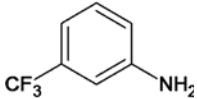
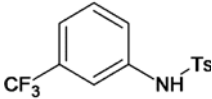
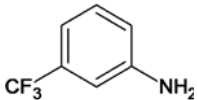
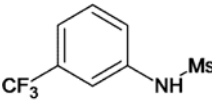
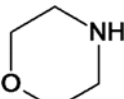
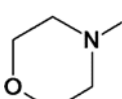
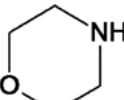
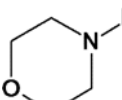
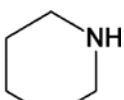
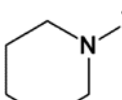
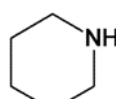
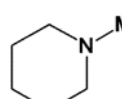
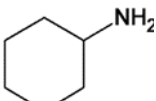
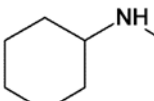
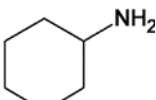
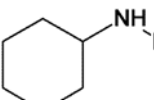
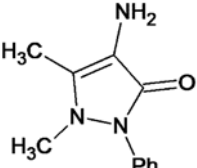
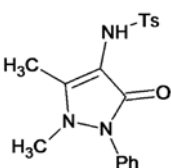
Reaction with different amino compounds :

The sulfonation reaction was carried out with different amino compounds using TsCl and MsCl as the sulfonylating agent in the presence of CTAB. All the amines showed rapid conversion within 15–45 minutes (Entries 1-23, Table 4) and bis-sulfonylated

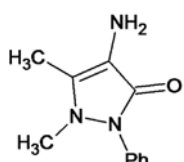
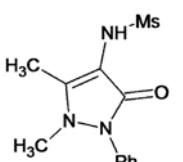
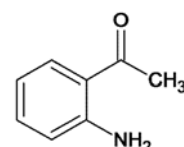
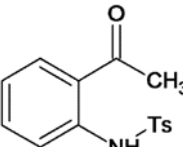
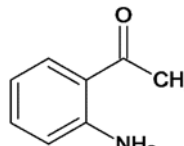
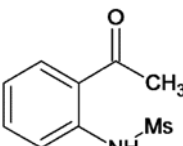




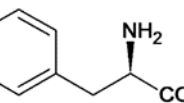
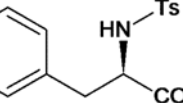
TABLE 4.*N*-Sulfonylation of various amines in aqueous solution of CTAB (0.05 mol.dm⁻³) at 303 ± 1K

Entry	Amino Compounds	Sulfonylated Products	Time (min)	Isolated Yield (%)	
				Without CTAB	With CTAB
1			20	65	92
2			25	62	88
3			20	63	90
4			25	61	87
5			30	65	86
6			35	62	87
7			25	68	91
8			30	66	92

(Table-4 Contd.)

9			25	68	94
10			25	65	91
11			15	58	93
12			15	56	87
13			15	66	94
14			15	63	90
15			15	56	93
16			15	55	93
17			25	58	90

(Table-4 Contd.)

18			20	53	88
19			20	63	92
20			25	65	89
21			50	25	70
22			50	18	58
23			50	20	85

product formation was not observed even with sterically hindered amines (Entries 17-20, Table 4). In the case of ethanol amine *N*-sulfonated product was obtained exclusively and no formation of the *O*-sulfonated product was detected. *N*-sulfonation of L (-) phenyl alanine was also carried out and it was found that only *N*-tosylation product was obtained with good isolated yield (Entry 23, Table 4).

Orientation of L (-) phenyl alanine in CTAB micelle :

The orientation of L (-) phenyl alanine in the CTAB micelle was studied by $^1\text{H-NMR}$ and results are shown in Table 5. A large change in chemical shift difference ($\Delta\delta$) of proton of phenyl ring and $-\text{CH}_2$ group of L (-) phenyl alanine indicates these groups

TABLE 5.

Shift in the δ values of L (-) phenyl alanine in CTAB micelle.

Proton type	$\Delta\delta$
Ortho	0.016
Meta	0.013
Para	0.012
-CH ₂	0.013
-CH	0.006

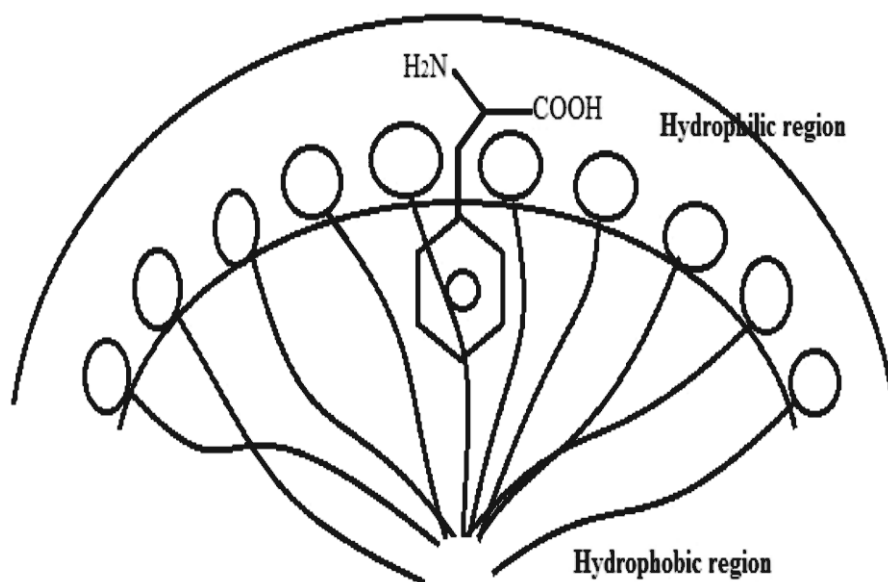


Fig. 6. Orientation of L (-) phenyl alanine in CTAB micelle

are present in the core of the micelle, while -CH group along with -NH₂ and -COOH groups are orient towards the bulk aqueous region as shown in Fig. 6.

CONCLUSIONS

CTAB was found to be a very efficient catalyst for the monosulfonation of various

amines, ethanol amine and L (-) phenyl alanine in aqueous media at 303 ± 1 K. This results several advantages such as shorter reaction time, mild reaction conditions, good stereoselectivity as well as chemoselectivity and high isolated yield. $^1\text{H-NMR}$ of L (-) phenyl alanine in CTAB micellar solution suggests that the phenyl ring is incorporated in the core of CTAB micelle. The rate of sulfonamide formation in water was increased by three folds, by addition of CTAB.

ACKNOWLEDGMENTS

B. V. Pawar is greatly thankful to the University Grant Commission (UGC), New Delhi, India, for providing a research fellowship.

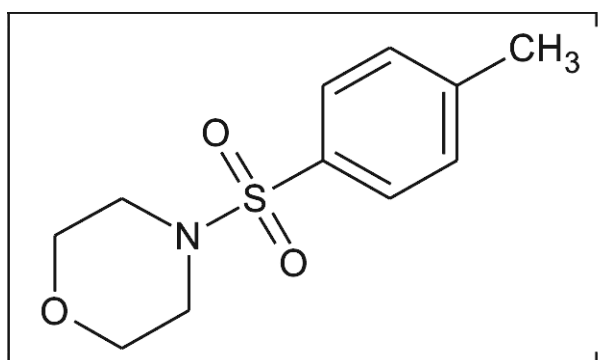
REFERENCES

1. C. Li, *J. Chem. Rev.*, 93, 2023 (1993).
2. P. A. Grieco, *Organic synthesis in water*. Blacky Academic and Professional : London (1998).
3. E. H. Cordes, *Reaction kinetics in micelles*. Plenum Press New York (1973).
4. S. K. Gangwar and M. Z. A. Rafiquee, *Int. J. Chem. Kinetics*, 638 (2007).
5. J. J. Shrikhande, M. B. Gawande and R. V. Jayaram, *Tetrahedron Lett.*, 49, 4799 (2008).
6. U. C. Nagaonkar and S. S. Bhagwat, *Ind. Eng. Chem. Res.*, 46, 1923 (2007).
7. A. S. Chhatre, R. A. Joshi and B. D. Kulkarni, *J. Col. and Int. Sci.*, 158, 183 (1993).
8. B. S. Samant, Y. P. Saraf and S. S. Bhagwat, *J. Col. and Int. Sci.*, 302, 207 (2006).
9. D. A. Jaeger and J. Wang, *Tetrahedron Lett.*, 33, 6415 (1992).
10. K. N. Ganesh, P. Mitra and D. Balsubramanian, *J. Phy. Chem.*, 86, 4291 (1982).
11. P. Mukerjee, *J. Pharma. Sci.*, 60, 1531 (1971).
12. B. S. Valaulikar, B. K. Mishra, S. S. Bhagwat and C. Manohar, *J. Col. and Int. Sci.*, 144, 304 (1991).
13. C. Hansch, G. Sammes and J. Taylor, *The rational design, mechanistic study and therapeutic application of chemical compounds*, volume 2. Comprehensive Medicinal Chemistry and Pergamon Press : Oxford (1990).
14. H. Yoshino, N. Ueda, J. Nijima, H. Sugumi, Y. Kotake, N. Koyanagi, N. Yoshimatsu, M. Asada, T. Watanabe, T. Nagasu, K. Tsukahara, A. Iijima and K. Kitoh, *J. Med. Chem.*, 35, 2496 (1992).
15. R. Pandey, T. Murashima, L. Tedeschi and A. Barrett, *J. Org. Chem.*, 68, 8274 (2003).

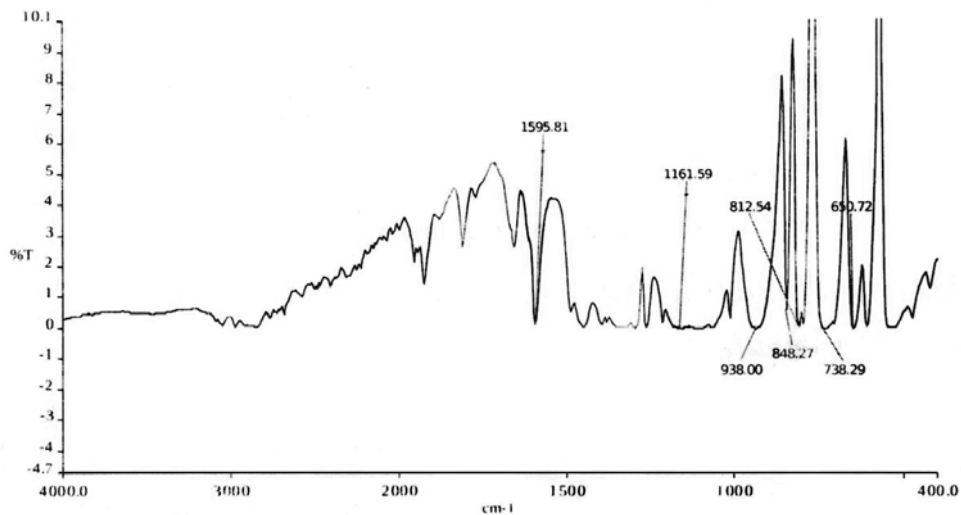
16. K. K. Andersen and D. N. Jones, *Comprehensive Organic Chemistry*, Vol. 3, Pergamon Press, Oxford (1979).
17. A. Yasuhara, M. Kameda and T. Sakamoto, *Chem. Pharm. Bull.*, 47, 809 (1999).
18. M. Surman, M. Mulvihill and M. Miller, *Org. Lett.*, 4, 139 (2002).
19. C. Goldenberg, R. Wandestrück and J. Richard, *Eur. J. Med. Chem.*, 12, 81 (1977).
20. M. Medebielle, O. Onomura, R. Keirouz, E. Okada, H. Yano and Terauchi, *Synthesis*, 17, 2601 (2002).
21. W. Hu, Z. Guo, F. Chu, A. Bai, X. Yi, G. Cheng and J. Li, *Bioorg. Med. Chem.*, 11, 1153 (2003).
22. X. Diang and N. S. Mani, *Green Chem.*, 8, 835 (2006).
23. R. Sridhar, B. Srinivas, V. Pavankumar, M. Narender and K. Ramarao, *Adv. Synth. Cat.*, 349, 1873 (2007).
24. S. Otto, J. B. F. N. Engberts and J. C. T. Kwak, *J. Am. Chem. Soc.*, 120, 9517 (1998).
25. T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem. Int. Ed.*, 44, 7174 (2005).
26. B. Gao, Q. Liu and L. Jiang, *Chem. Engg. and Processing : Process Intensification*, 47, 852 (2008).
27. K. C. Kuperkar, *Coll. and Surf. A : Physicochem. Eng. Aspects*, 380, 60, (2011).
28. C. A. Bunton, *Adv. Col. and Int. Sci.*, 123–126, 333 (2006).
29. C. Siswanto and J. F. Rathman, *J. Col. and Int. Sci.*, 196, 99 (1997).

SUPPORTING INFORMATION :

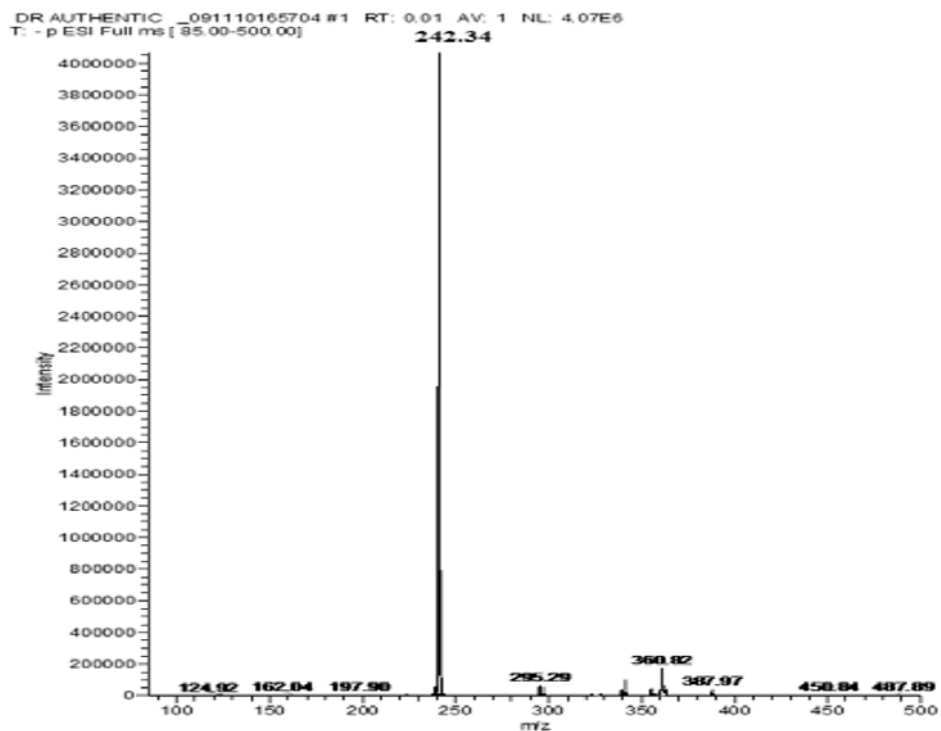
COMPOUND : 11



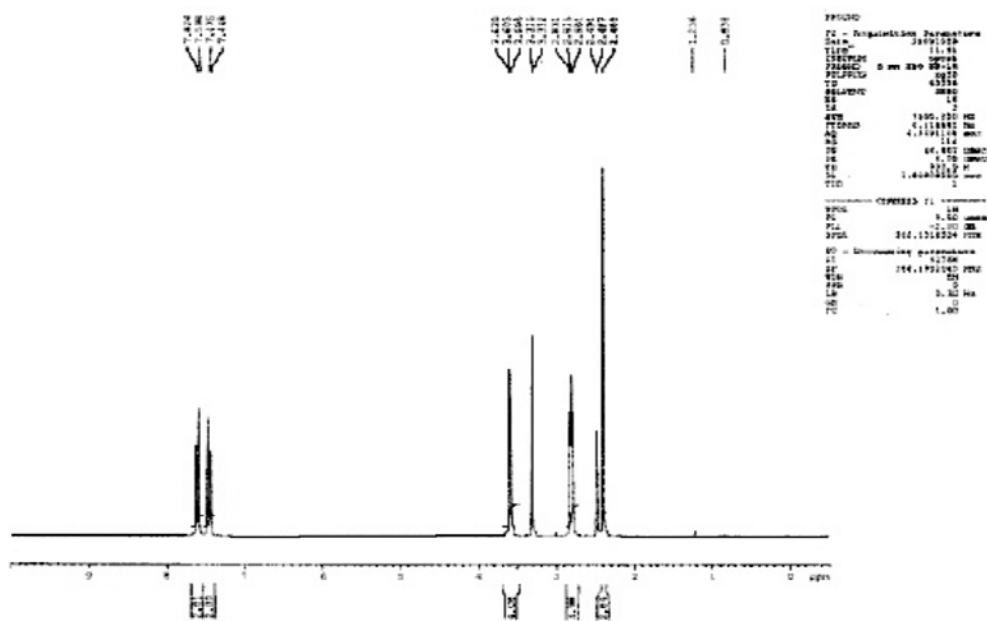
IR



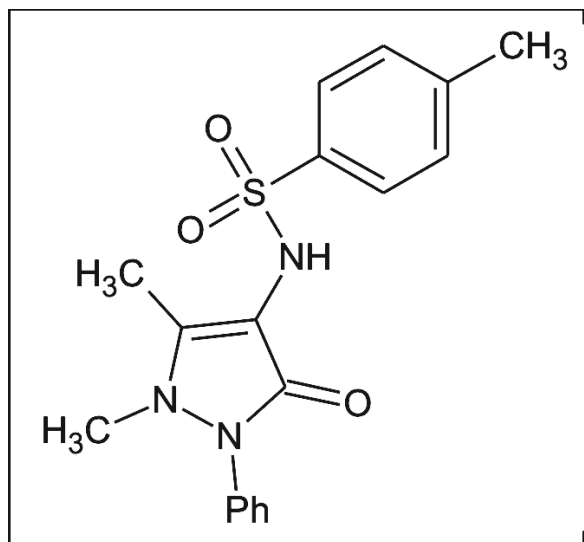
MASS



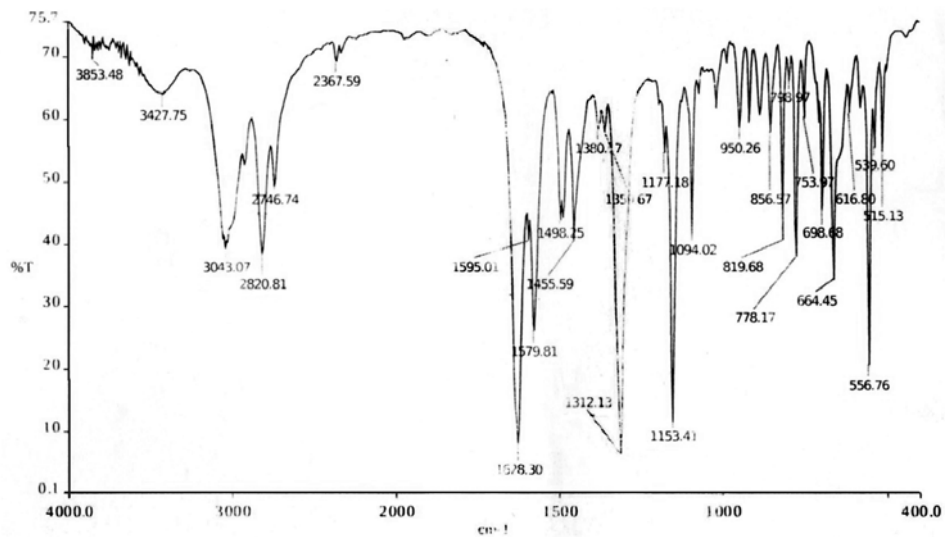
¹H-NMR



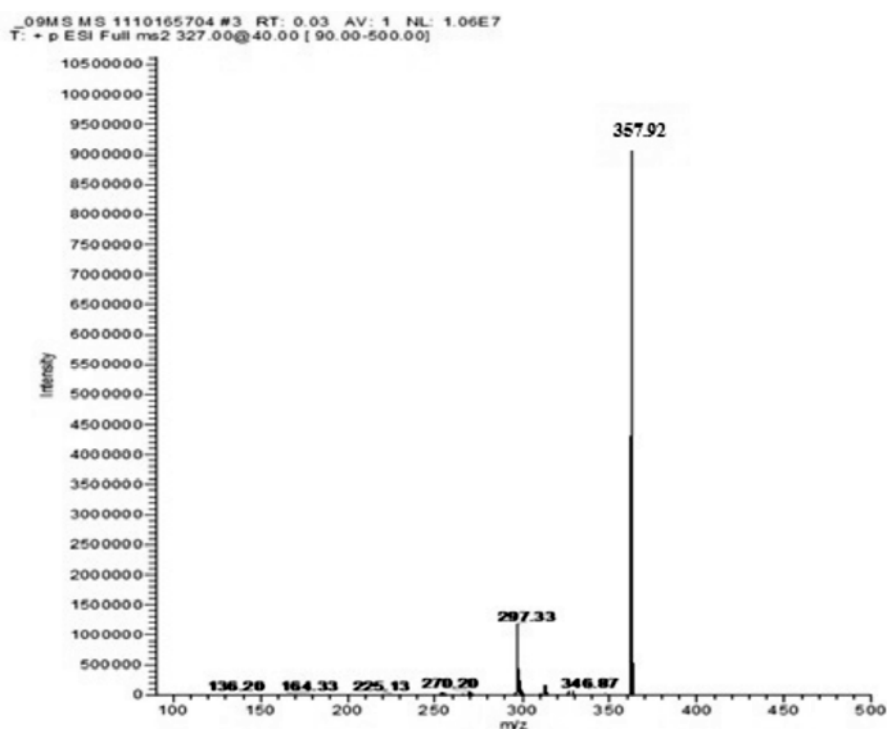
COMPOUND : 17



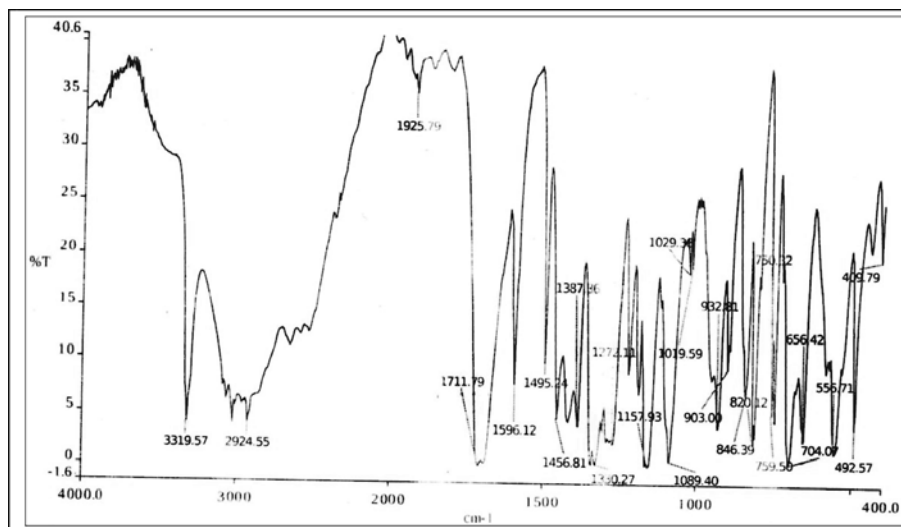
IR



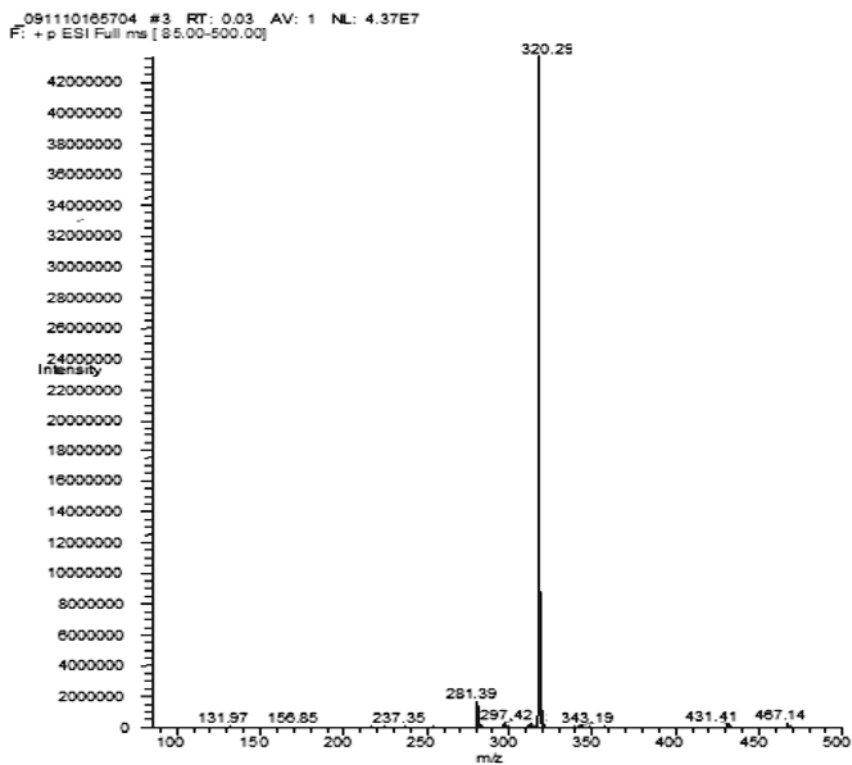
MASS



IR



MASS



¹H-NMR

