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N-alkylation of azoles disubstituted acetamides under microwave and Mannich reaction conditions

Ambarsing P. Rajput*[a] and Rambhau P. Gore[b]

[a]*Department of Chemistry P.G. Research Centre, Z. B. Patil College, Dhule, 424002 (M.S.) India*
[b]*School of Chemical Technology, North Maharashtra University, Jalgaon, 425001 (M.S.) India*

ABSTRACT

The N-alkylation of some secondary amides, 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamides, was carried out under different conditions basic, microwave and Mannich reaction. The attempts of alkylation of secondary amides using strong bases were unsuccessful. These prompted us to apply microwave and Mannich reaction.

Key words: Azoles, ethyl bromoacetate, Phase transfer catalysts, microwaves.

INTRODUCTION

N-alkylation of an amide is an important transformation in organic synthesis, which converts primary and secondary amides to tertiary amides, has been practiced for decades. It is also a useful method of construction of heterocyclic molecules in multi-step organic synthesis [1]. The amide functionality is an important unit among the naturally occurring and synthetic organic molecules, while N-alkylation is the method of modification of the biological activities of drugs. It also protects the base labile proton of amide in multi-step organic synthesis and several other functional groups such as alcohols, amines, carboxylic acids and α-carbon are protected by alkylation reactions [2].The neutral amide generally reacts with electrophilic alkylating reagents at basic oxygen atom under the kinetic control and no N-alkylation observed [3]. In order to have N-alkylation over the O-alkylation, the more basic site of alkylation in amides, amides are first being converted to their conjugate bases, amide anion, using strong bases[4] also reports are that alkylation under basic conditions are synthetically most important[5]. So bases are inevitable in N-alkylation. In presence of bases amide group reactivity and orientation is determined by the stability of anions [6]. Various bases used either in conventional way or using phase transfer catalysts (PTC) in stoichiometric amount[7] or in excess are KOH, K_2CO_3, Na(s), NaOMe, NaOEt, t-BuOk, NaH, $NaNH_2$, DIEA and n-BuLi while the PTC used are TBAB (tetrabutylammonium bromide), tetraethylammonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, triethylbenzylammonium bromide and cetyltrimethylammonium bromide[8].

The selectivity and yield of product also largely depends on nature of solvent in alkylation [9]. Generally increase in polarity of solvent, reactivity increases but at the same time selectivity of product formed was found to decreases [10]. Generally solvents used are DMSO, DMF, THF, ethylacetate, toluene, n-hexane, dichloromethane, acetone, AcN, or mixture of solvents like DMSO: AcN [11].

MATERIALS AND METHODS

All chemicals used are of analytical grade and solvents were distilled prior to use. Melting points are uncorrected. FTIR spectra were recorded on Shimadzu-8400 FTIR spectrometer. ^{1}H NMR spectra were recorded on 400 MHz Varian NMR Instrument model Mercury plus spectrometer and their chemical shifts are reported in δ values in ppm. Mass spectra were obtained with Waters acquity UPLC TQ Detector Mass spectrometer.

Procedure for the synthesis of N-(2-bromoethyl)-2-(1H-azol-1-yl)-N- (substituted phenyl) acetamide 3a-d(i-ii)-6a-d(i-ii)

To a solution of 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamide **2a(i-ii)-2d(i-ii)** (5 mmol) in dry ethanol(30 ml) excess of sodium ethoxide (0.48 g, 7 mmol) was added and stirred for 30 min at rt. Alkylating agent, dibromoethane (0.45 ml, 5 mmol) was added slowly. The reaction mixture was then refluxed at 60 ^{0}C for 6 h., applying anhydrous $CaCl_2$ guard tube. The progress of reaction was monitored by TLC. Refluxing was continued for another 8 h. The reaction mixture was allowed to attain rt, treated with water, concentrated on rotary evaporator. The products obtained were analyzed by IR.

The similar reaction was repeated with increase in temperature to 70 ^{0}C and refluxing was time increased from 18 to 22 h. but the reaction could not standardize.

Procedure for the synthesis of N-(2-bromoethyl)-2-(1H-azol-1-yl)-N- (substituted phenyl) acetamide 3a-d(i-ii)-6a-d(i-ii)

A clear solution of 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamide **2a(i-ii)-2d(i-ii)** (0.01 mol) was prepared in dry THF: DMF (10:1, 33 ml) to this dibromoethane (3.75 ml, 0.02 mol) was added in a drop wise fashion and stirred for 30 min. Finally NaH (60% dispersion in mineral oil) (1.3 g, 0.03 mol) was added slowly.

Reaction mixture was then stirred for 20 min. at rt. and then refluxed using guard tube at 60 ^{0}C for 9 h. on water bath. The progress of reaction was monitored by TLC, refluxing was continued for another 6 h. The reaction mixture was allowed to attain rt, filtered , mother liquid was treated with distilled water (40 ml), extracted with dry ether, ether layer dried with Na_2SO_4 and evaporated while the residue was dried by using IR lamp. The products were checked by IR spectroscopy and mp. In this case no expected or any other product was detected but the starting material was reappeared.

The reaction was repeated for other amides using only dry DMF, increase in temperature by 10 ^{0}C, and refluxing time was increases to 20-22 h.

Procedure for the synthesis of ethyl 2-[2-(1H-azol-1-yl)-N-phenyl acetamido]acetate 7a(i-v)-7d(i-v)

To a large size (500 ml) borosil conical flask, powdered KOH (1.12 g, 20 mmol), K_2CO_3 (2.70 g, 20 mmol), and PTC, TBAB (0.16 g, 0.50 mmol) were taken, to this 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamide **2a(i-v)-2d(i-v)** (5 mmol) was added and stirred by glass rod. Alkylating agent ethyl bromoacetate (EBA) (0.80 ml, 7 mmol) was added in a drop wise fashion. The flask was plugged with loose cotton and irradiated in a microwave oven for 30-150 sec. at 180 power. Reaction mixture was allowed to cool, treated with distilled water (50 ml) and extracted with diethyl ether.

ethyl 2-[2-(1H-imidazol-1-yl)-N-(2-chlorophenyl) acetamido] acetate 7a(iv). Colorless needles, yield 52%, mp 128-130 ^{0}C, IR (ν max, cm^{-1}): 1730(C=O, ester), 1656(C=O, amide), 1259, 1103, 752 (ortho disub.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0 (3H, t, CH_3), 3.38(2H, q, CH_2), 4.83(2H, s, CH_2), 5.22(2H, s, CH_2), 7.54-7.12(7H, m, Ar-H). LCMS (*m/z*, %): 346.3 [M^+ + Na +2, 3], 242.0 (Imi-N + CH_2, 100).

ethyl 2-(2-(1H-benzimidazol-1-yl)-N-(4-chlorophenyl) acetamido)acetate 7b(v). Straw color crystals, yield 58%, mp 122-124 ^{0}C, IR (ν max, cm^{-1}): 3091, 2812, 1697(C=O, ester),1627(C=O, amide), 1097, 844 (para disub.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (3H, t, CH_3), 3.90(2H, q, CH_2), 4.95(2H, s, CH_2), 5.19(2H, s, CH_2), 7.64-7.18(9H, m, Ar-H).

ethyl 2-(2-(1H-benzotriazol-1-yl)-N-(2-chlorophenyl) acetamido)acetate 7c(iv). Yellow crystals, yield 61%, mp. 202-204 ^{0}C, IR (ν max, cm^{-1}): 3095, 2930, 1727(C=O, ester), 1659(C=O, amide), 748(ortho disub.). ^{1}H NMR (400

MHz, DMSO-d_6): δ 1.22 (3H, t, CH_3), 3.82(2H, q, CH_2), 5.59(2H, s, CH_2), 6.05(2H, s, CH_2), 8.25-7.34(8H, m, Ar-H). LCMS (*m/z*, %): 372.00 [M^+, 4]

ethyl 2-(2-(4-methylpiperazin-1-yl)-N-phenyl acetamido)acetate 7d(i). Colorless crystals yield 64%, mp. 182-184 ^{0}C, IR (ν max, cm^{-1}): 3190, 2958, 2872, 1730(C=O, ester), 1672(C=O, amide), 1166, 760, 736(mono sub.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (3H, t, CH_3), 3.10(2H, q, CH_2), 1.88(8H, s, $4CH_2$), 2.90(3H, s, N-CH_3), 4.35(2H, s, CH_2), 5.21(2H, s, CH_2), 7.32(5H, s, Ar-H). LCMS (*m/z*, %): 342.40[(M^++Na), 4], 242.4(18), 239.1(100), 141.9(3).

Procedure for the synthesis of 2-(1H-imidazol-1-yl)-N-(morpholinomethyl)-N-(substituted phenyl) acetamide 8a(i-v)-8d(i-v)

Active H-atom compound, 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamide **2a(i-v)- 2d(i-v)** (4 mmol) was dissolved in dry ethanol (100 ml). To this, cold morpholine (0.35 ml, 4 mmol) and a drop of conc. hydrochloric acid were added with constant stirring, followed by formaldehyde (1 ml, 0.03 mol) was added and reaction mixture was refluxed for 15-18 h. It was allowed to attain rt, extracted with EA/AcN/ether to get the desired product.

2-(1H-benzimidazol-1-yl)-N-(morpholinomethyl)-N-(2-chlorophenyl) acetamide 8b(iv). Colorless crystals, yield 55%, mp 152-154 ^{0}C, IR (ν max, cm^{-1}): 3190, 2958, 1672, (C=O, amide), 1599, 736 (ortho disub.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05 (4H, m, $2CH_2$), 3.75 (4H, m, $2CH_2$), 4.81(2H, s, CH_2), 5.39 (2H, s, CH_2), 7.60-7.18(9H, m, Ar-H). LCMS (*m/z*, %): 335.0 [M^+-35 (-Cl), 7], 211.0 (18), 129 (100).

2-(1H-benzotriazol-1-yl)-N-(morpholinomethyl)-N-phenylacetamide 8c(i). Light brown crystals, yield 54%, mp 193-195 ^{0}C, IR (ν max, cm^{-1}): 3088, 2987, 1691(C=O, amide), 1610, 1437, 1247, 736(mono sub.).

2-(4-methylpiperazin-1-yl)-N-(morpholinomethyl)-N-phenylacetamide 8d(i). Curdy crystals, yield 59%, mp 178-181 ^{0}C, IR (ν max, cm^{-1}): 3110, 2929, 2798, 1693(C=O, amide), 1250, 760, 735(mono sub.). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 2.28 (8H, s, $4CH_2$), 2.70 (3H, s, N-CH_3), 2.32 (4H, m, $2CH_2$), 2.89 (4H, m, $2CH_2$), 4.20 (2H, s, CH_2), 5.10 (2H, s, CH_2), 7.24 (5H, s, Ar-H). LCMS (*m/z*, %): 332.0 (M^+, 5), 248.1 (100), 249.1(28).

2-(4-methylpiperazin-1-yl)-N-(morpholinomethyl)-N-(4-chlorophenyl) acetamide 8d(v). Pale yellow crystals, yield 67%, mp 166-168 ^{0}C, IR (ν max, cm^{-1}): 3180, 2949, 2704, 1666 (C=O, amide), 1138 (C-O-C), 823 (para disub.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (8H, s, $4CH_2$), 2.82 (3H, s, N-CH_3), 3.7-3.18 (8H, m, morpholine-H), 4.30 (2H, s, CH_2), 4.90 (2H, s, CH_2), 7.50-7.20(4H, dd, Ar-H). LCMS (*m/z*, %): 268.1 (4), 248.1 (100), 249.1(34), 113.0 (3).

Table I. Results of antimicrobial activities of compounds 7a-d and 8a-d.

Compound No.	Antimicrobial activity*			
	E. coli	***S. aureus***	***C.albicans***	***A. niger***
7a(iv)	_	16.00	_	9.85
7b(v)	_	_	_	_
7c(iv)	_	_	_	_
7d(i)	_	_	_	_
8b(iv)	_	_	_	_
8c(i)	_	_	_	_
8d(i)	_	_	_	_
8d(v)	_	_	_	_
Chloramphenicol	16.91	18.79	**NA**	**NA**
Amphotericin-B	**NA**	**NA**	14.23	15.34

Antimicrobial activity

The synthesized compounds were screened for their in vitro antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger* by Disc diffusion method (Well method, Disc size 6mm, Hi media) using Nutrient agar, Potato dextrose agar and MGYP. The agar diffusion assay (Well method, Disc size 6mm, Hi media) was used. The compounds were tested at the concentration of 100 µg/ml in DMF. The results were compared with standards Chloramphenicol, Streptomycin and Amphotericin-B. The zones of inhibition were measured in mm and the data is presented in Table 1. The results of tertiary amides were compared with corresponding secondary amides, Table 2.

Table II. Results of antimicrobial activities of compounds 2a-d.

Compound No.	Antimicrobial activity*			
	E. coli	*S. aureus*	*C.albicans*	*A. niger*
2a(iv)	8.1	9.55	_	_
2b(v)	17.38	20.43	11.11	_
2c(iv)	_	_	_	_
2d(i)	9.65	11.13	_	9.39
2b(iv)	12.19	15.03	_	_
2c(i)	12.19	10.20	9.30	14.07
2d(v)	9.66	9.57	9.45	13.38
Streptomycin	18.22	20.12	**NA**	**NA**
Amphotericin-B	**NA**	**NA**	14.23	15.34

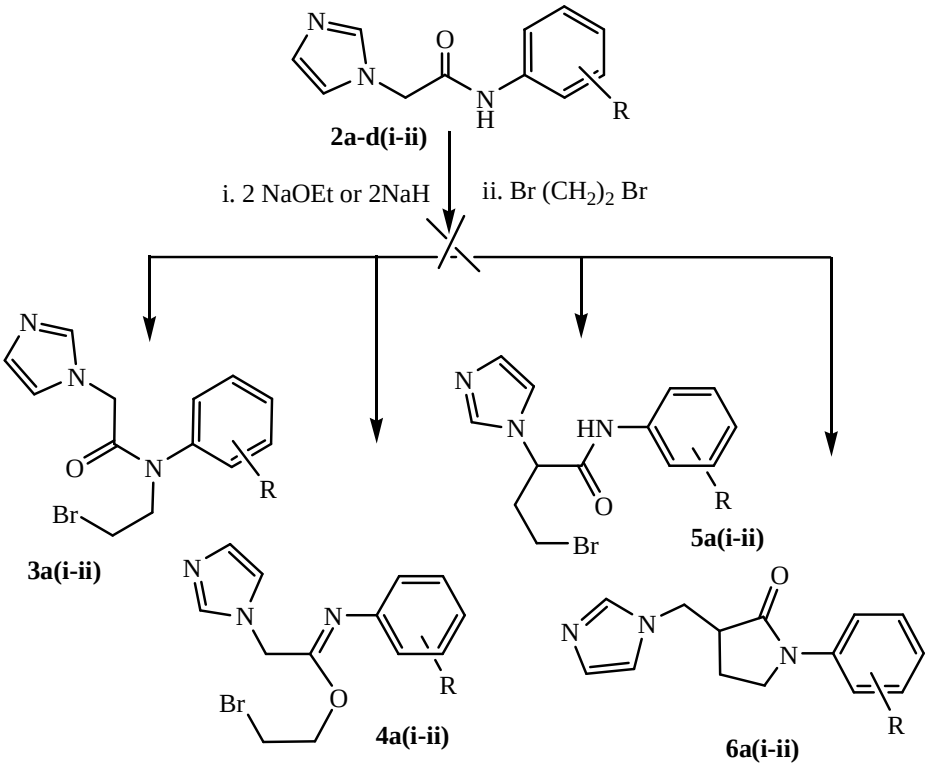
*Diameter in mm calculated by digital Vernier Caliper, * Zone of inhibition in mm. '_' means no zone of inhibition.* ***NA****- Not applicable*

The antimicrobial activity data showed that the secondary amides are biological active while the activity removed as such when converted to tertiary one. This may be due to removal of active hydrogen atom.

RESULTS AND DISCUSSION

Literature survey reveals that neither the synthesis of 2-(1H-azole-1-yl)-N-(substituted phenyl) acetamide nor their N-alkylation has been reported. Some studies on N-alkylation of amides have shown the complex nature of N-alkylation reaction, majority of methods are having limitations such as harsh reaction condition, functional group tolerance, low yield and less selectivity, along with N-alkylation facilitates O-alkylation, C-alkylation and C, N-dialkylation due to ambident properties of amide anions. Relatively few reports are on studies of anions in which there is competition between C and heteroatom usually O, N, S have been reported.

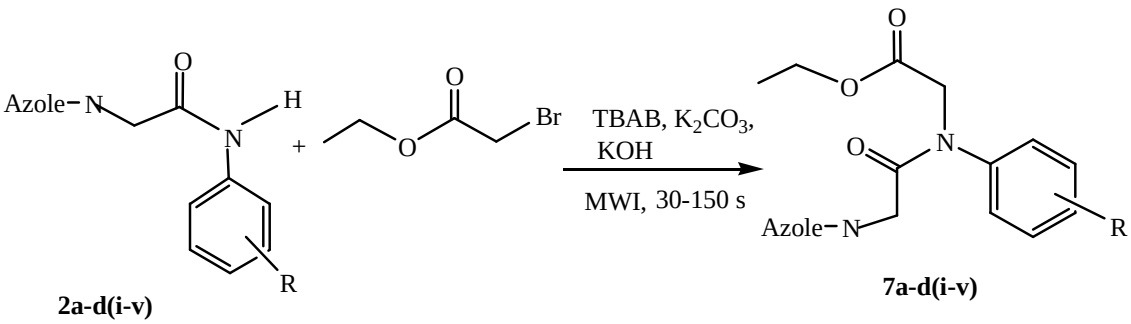
Considering all the possibilities of N-alkylation we tried alkylation in some azole amides 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamide **2a(i-ii)-2d(i-ii)** treating with strong bases like NaOEt, NaH **(Scheme 1)**.



Scheme 1

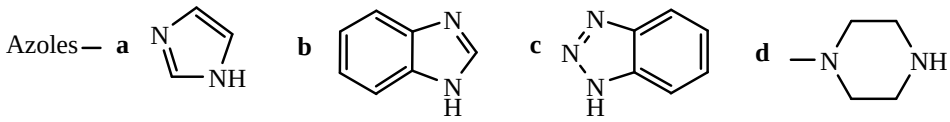
The similar reactions were repeated with increase in temperature by 10^0C, refluxing time by 4 h. and used of alternative solvents but the reaction could not standardize. These prompted us to apply microwave and Mannich reactions. Microwave assisted organic reactions are now well established and considered as green reactions[12], microwave reactions with PTC have many advantages over conventional reactions and eliminates[13] —a) Use of hazardous, toxic solvents. b) Complex work up when aprotic organic solvents with high water solubility and high bp. are used. c) Use of hazardous reagents such as metal hydrides. d) Long reaction procedure at reflux. Moreover PTC have more selectivity, avoids formation of by products.

On the same line, we applied Mannich reaction for N-alkylation of amides which absolutely led to N-alkylation over the C or O-alkylation with the introduction of amino substituted alkyl group [14]. The PTC microwave assisted N-alkylation of **2a-d (i-v)** by ethyl bromoacetate in presence of excess bases undergone smoothly within 30-150 sec. leading to the formation of desired N-(2-bromoethyl)-2-(1H-azol-1-yl)-N- (substituted phenyl) acetamide **7a-d(i-v)** in moderate yields **(Scheme 2)**.



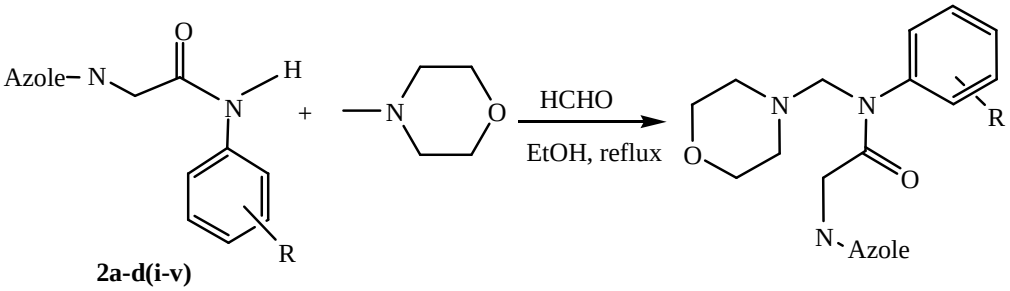
2a-d(i-v) **7a-d(i-v)**

R: i =H, ii =-2 CH_3, iii=-4 CH_3 , iv =-2 Cl, v = -4 Cl



Scheme 2

Similarly **2a-d (i-v)** were converted to N-morpholinomethyl derivatives **8a-d(i-v)** applying classical Mannich reaction in azoles disubstituted acetamides **(Scheme 3)**.



2a-d(i-v) **8a-d(i-v)**

R: i =-H, ii =-2 CH_3, iii =-4 CH_3, iv =-2 Cl, v = -4 Cl

Scheme 3

CONCLUSION

The study evaluates the fundamental organic reaction, N-alkylation, in newly synthesized some azoles based secondary amides. The amides are N-alkylated using non conventional protocol, microwave assisted reaction, and successfully applied the Mannich reaction. The synthesis strategy is proved simple in ambident nature substrate and selectively yields tertiary amides in moderate yields. The attempts using strong bases were unsuccessful. The antimicrobial study of alkylated amides carried out against the selected strains. The comparative antimicrobial data of secondary amides with alkylated tertiary amides showed modification in activities.

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REFERENCES

[1] B. C. Challis, J. A. Challis; The Chemistry of Amides, Zabicky, J. Eds, Inter science London, **1970**, 731.
[2] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell; Vogel's Texbook of Practical Organic Chemistry, Wiley, New York, **1989**, 5, 916. (b) I. A. Rivero, L. Guerrero, K. A. Espinoza, M. C. Meza, J. R. Rodriguez, *molecules*, **2009,** 14, 1860.
[3] Alan. R. Katritzky, M. Drewniak, P. Lue, *J. Org. Chem.*, **1988,** 53, 5854.
[4] A. V. Kurkin, D. S. Belov, M. A. Yurovskaya, *Chem. Hetrocycl. Compounds*, **2008,** 44, 9, 1123.
[5] Alan R. Katritzky, M. Drewniak, *J. Chem. Soc. Perkin Trans 1*, **1988,** 2339.
[6] (a) R. A. W. Johnstone, M. E. Rose, *Tetrahedron*, **1979,** 35, 2169. (b) Neal O. Brace, *J. Org. Chem.*, **1993,** 58, 1804.
[7] A. V. Karchava, I. S. Shuleva, A. A. Ovcharenko, M. A.Yurovskaya, *J. Heterocycl. Compounds*, **2010,** 46, 3, 291.
[8] (a) R. Radinov, C. Chanev, M. Haimova, *J. Org. Chem.*, **1991,** 56, 4793. (b) A. Brik, Chung-Yi Wu, M. D. Best, Chi-Huey Wong, *Bioorg. Med. Chem.*, **2005,** 13, 4622.
[9] S. Ferrer, D. P. Naughton, I. Parveen, M. D. Threadgill, *J. Chem. Soc. Perkin Trans 1*, **2002,** 335.
[10] A. R. Stein, See-Hua Tan, *Can. J. Chem.*, **1974,** 52, 4050.
[11] (a) O. I. Artyushin, E. V. Sharova, P. V. Petrovskii, I. L. Odinets, *Russian Chem Bull Int.* Edn., **2009,** 58, 1, 216. (b) F. Fache, L. Jacquot, M. Lamaire, *Tetrahedron lett.*, **1994,** 35, 20, 3313.
[12] A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, B. K Banik, *Synthesis*, **2002,** 1578.
[13] (a) M. Makosza, *Pure Appl. Chem.*, **2000,** 72, 7, 1399. (b)) I. A. Rivero, L. Guerrero, K. A. Espinoza, M. C. Meza, J. R. Rodriguez, *molecules*, **2009,** 14, 1860.
[14] a) B. Lingappa, K. S. Girisha, B. Kalluraya, N. S. Rai, N. S. Kumari, *Indian J. Chem.*, **2008,** 47B, 1858. (b) T. B. Shah, A. Gupta, M. R. Patel, V. S. Chaudhari, H. Patel, V. C. Patel, *Indian J. Chem.*, **2009,** 48B, 88. (c) K. C. Chaluvaraju, I. Bhat, *J. Indu. Council Chem.*, **2009,** 26, 1, 90.