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Synthesis, characterization and antimicrobial activity of N'-(substituted phenyl)-2-(1H-azol-1-yl) acetamides

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ABSTRACT

A facile two-step synthesis of N'-(substituted phenyl)-2-(1H-azol-1-yl) acetamides have been carried out by acylation of substituted aromatic primary amines and subsequent alkylation of N-chloroacetyl aryl amineswith some azoles in good yields. The synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data.

Keywords: acylation, aryl amines, alkylation, azoles,antimicrobial activity.

INTRODUCTION

It is well known that many bioactive compounds are found as amide derivatives[1]. Many natural products such as proteins and peptides are having linear structures of cyclic polyamides. Heterocyclic carboxamides are important bioactive agent showing activity as antimicrobial[2], melatonin analogs, potential anti-HIV drugs [3], antitumor agents[4] and antipsychotic agents [5].Various substituted amide derivatives are associated with antimicrobial, analgesic[6], anticonvulsant[7], antiulcer[8], cardiotonic [9], MAO inhibitor, anti-inflammatory[10], sodium channel blockers. They are also known to possess CNS activities such as antipsychotic, analgesic, anticonvulsants and antidepressant. Literature survey indicates that many anticonvulsants contain amide group as an important pharmacophore [11]. Nicotinamide analogue, pyrazinamide has been used for almost 50 years as a first-line drug to treat tuberculosis [12]. Amides of dicarboxylic acids are widely used as herbicides, defoliants, insecticides, fungicides and repellants [13].Amides are known to play vital role in molecular recognition these works as DNA recognizing molecules through amide proton hydrogen bonding like synthetic analogues of distamycin and neutropsin [14].Amides are used as building blocks for many bioactive compounds such as vitamins, agrochemicals, xanthenes, combinatorial peptide synthesis, oligocarbamates, oligoamides, β-lactams, polyenamides, and benzodiazepines [15].

In view of the wide and variety of useful biological activities, therapeutic and agrochemical applications, we have planned to synthesize novel amides using potential biological active substrate azoles. Numbers of synthetic approached have been reported for the synthesis of carboxamides, but these procedures suffers limitations such as harsh reaction condition, functional group tolerance and relatively low yield. The acylation-alkylation procedure found to worthwhile in this context.

MATERIALS AND METHODS

Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu-8400 spectrophotometer. ^{1}H NMR were recorded on Varian, USA Mercury Plus 300 MHz NMR spectrometer and ^{13}C NMR were recorded on 400 MHz Varian NMR instrument, chemical shift are reported in δ values in ppm. Mass

spectra were obtained with Waters acquity UPLC TQ Detector spectrometer. The progress of reaction and purity of compounds were checked by TLC.

Synthesis of N-chloroacetyl aryl amines

Chloroacetylchloride (0.05mol, 4.0mL) and TEA (triethylamine) (0.025 mol) were taken in dry toluene (30mL) and the clear solution was stirredfor 15 min. To this solution various substituted aromatic primary amines (0.04mol) dissolved in dry toluene were added in a drop wise fashion and refluxed on water bath for 2h. The reaction mixture was allowed to cool. It was then filtered and recrystallized from ethanol.

Synthesis of2-(1H-azol-1-yl)-N-(substituted phenyl) acetamides (1a,b,c 2a,b,c 3a,b,c)

A solution of azoles **(1,2,3)**(0.05mol) in acetone was slowly added to a solution of N-chloroacetyl aryl amines (0.045 mol) and activated K_2CO_3 (0.015 mol, 2.0g) in acetone (30mL).The reaction mixture was refluxed for 10-14 h. on water bath which was then allowed to cool and kept overnight. The residue obtained was filtered, washed with water and recrystallized from suitable solvent to obtained **1a,b,c 2a,b,c** and **3a,b,c.**

2-(1H-imidazol-1-yl)-N-phenyl acetamide(1a)

Colorless crystals, 74% yield, mp 218-221 ^{0}C; IR: cm^{-1} 3236 (NH), 1649 (CO), 757 and 690 (mono sub. ring) ; ^{1}H NMR (DMSO-d6): δ 10.78 (s, 1H, NH), 7.65-7.00 (m, 8H, Ar-H), 5.10 (s, 2H, CH_2) ; ^{13}C NMR (DMSO-d6): δ 165 (CO), 139, 138, 128, 123, 120, 118 (Ar-C &Imi.-C), 40.23 (NCH_2CO); MS m/z : 199.2 (M^+-2).

2-(1H-imidazol-1-yl)-N-(4-methylphenyl) acetamide (1b)

Creamy solid, 65 % yield, mp144-145^{0}C; IR: cm^{-1} 3210 (NH), 3094, 2914, 1667 (C=O, amide), 1556, 817 (para disub.ring); ^{1}H NMR (DMSO-d6):δ 10.12(s, 1H, NH), 7.62-6.82(m, 7H, Ar-H), 4.82(s, 2H, CH_2), 2.21(s, 3H, Ar-CH_3) ; ^{13}C NMR (DMSO-d6): δ 166 (C=O), 138, 136, 134, 130, 129, 128, 124, 121, 120.84(Ar-C &Imi.-C), 48.90 (Ar-CH_3), 42 (NCH_2CO) ; MS m/z : 214.0 (M^+-1).

2-(1H-imidazol-1-yl)-N-(4-chlorolphenyl) acetamide (1c)

Curdy crystals, 68% yield, mp235-237^{0}C; IR: cm^{-1} 3537 (NH), 3170, 3130, 2952, 1678 (C=O), 831 (para disub. ring) ; ^{1}H NMR (DMSO-d6): δ 10.67(s, 1H, NH), 8.12 (s, 1H, imi.C_2-H), 7.75-7.20(m, 6H, Ar-H), 5.12 (s, 2H, CH_2); ^{13}C NMR (DMSO-d6): δ 165.2 (C=O), 140.35, 139, 131, 129.10, 125, 124, 122, 121.7 (Ar-C), 42.20(NCH_2CO); MS m/z : 234.4 (M^+-1).

2-(1H-benzimidazol-1-yl)-N-phenyl acetamide (2a)

Colorless crystals, 69 % yield, mp242-244 ^{0}C; IR: cm^{-1} 3312 (NH), 3022, 2924, 1642 (C=O), 760, 714 (mono sub. ring);^{1}H NMR (DMSO-d6): δ9.70 (s, 1H, NH), 7.17-7.49 (m, 10H, Ar-H), 3.30(s, 2H, CH_2); ^{13}C NMR (DMSO-d6):δ164.42 (C=O), 139, 137, 131.41,121.26, 120.57, 117, 115(Ar-C), 39.32 (NCH_2CO); MS m/z : 250.10 (M^+-1).

2-(1H-benzimidazol-1-yl)-N-(4-methylphenyl) acetamide (2b)

Colorless crystals, 72% yield, mp 238-241 ^{0}C; IR: cm^{-1} 3341 (NH), 3014, 2932, 1675 (C=O), 817 (para disub. ring); ^{1}H NMR (DMSO-d6): δ 8.77 (br s, 1H, NH), 7.33-6.82 (m, 9H, Ar-H) 3.35(s, 2H, CH_2), 2.26(s, 3H, Ar-CH_3); ^{13}C NMR (DMSO-d6): δ 165.5 (C=O), 139, 137, 133, 131, 125, 123, 121, 118, 117 (Ar-C & Benzimi.-C), 47.60 (Ar-CH_3), 45 (NCH_2CO); MS m/z : 264.0 (M^+-1).

2-(1H-benzimidazol-1-yl)-N-(4-chlorophenyl) acetamide (2c)

Colorless crystals, 62% yield, mp109-111^{0}C; IR: cm^{-1} 3412 (NH), 3036, 2877, 1649 (C=O), 842 (para disub. ring); ^{1}H NMR (DMSO-d6): δ9.35 (s, 1H, NH), 8.30 (d, 1H, benzimi.), 7.65-7.20 (m, 8H, Ar-H), 5.08 (s, 2H, CH_2);^{13}C NMR (DMSO-d6): δ 167 (C=O), 144, 137.19, 128.45, 127.74, 122, 121.20, 121, 118 (Ar-C),42.21(NCH_2CO); MS m/z : 284.20 (M^+-1).

2-(1H-benzotriazol-1-yl)-N-phenyl acetamide (3a)

Colorless needles, 78 % yield, mp 202-204^{0}C; IR: cm^{-1} 3262 (NH), 3054, 1676 (C=O), 756, 700 (mono sub. ring); ^{1}H NMR (DMSO-d6): δ 8.50 (s, 1H, NH), 7.42-6.85 (m, 9H, Ar-H), 3.43 (s, 2H, CH_2); ^{13}C NMR (DMSO-d6): δ 163 (C=O), 158, 135, 132.40,122.36, 119.27, 118 (Ar-C), 40.72 (NCH_2CO); MS m/z : 251 (M^+-1).

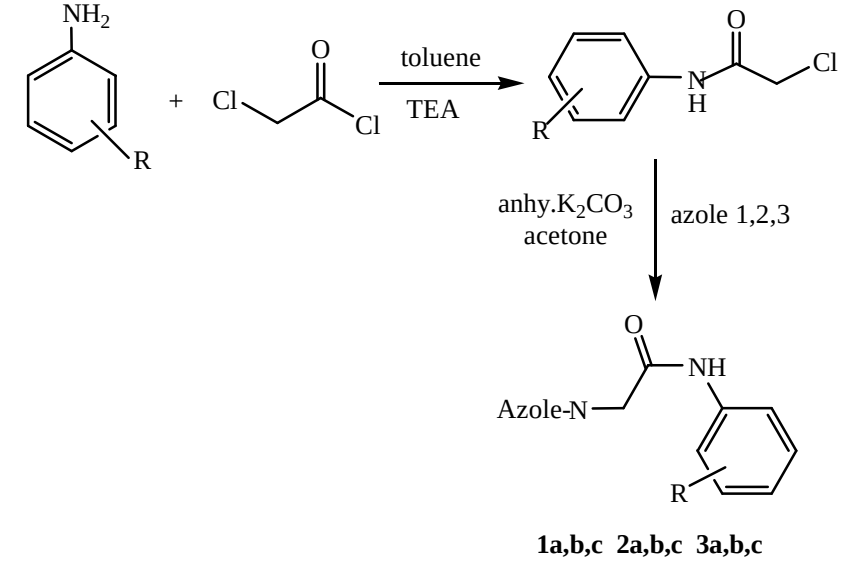
2-(1H-benzotriazol-1-yl)-N-(4-methylphenyl) acetamide (3b)

Colorless crystals, 62 % yield, mp230-233^{0}C; IR: cm^{-1}3347 (NH), 3190, 2938, 1649 (C=O), 817 (para disub. ring);^{1}H NMR (DMSO-d6): δ 8.53 (s, 1H, NH), 7.65-7.10 (m, 8H, Ar-H), 3.50 (s, 2H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (DMSO-d6): δ 165 (C=O), 140, 138, 132, 131, 126, 124, 121 (Ar-C), 44.20 (Ar-CH_3), 42 (NCH_2CO); MS m/z :266.10 (M^+).

2-(1H-benzotriazol-1-yl)-N-(4-chlorophenyl) acetamide (3c)
Reddish crystals, 72 % yield, mp242-244 ^{0}C; IR: cm^{-1} 3224 (NH), 3037, 2822, 1654 (C=O), 818 (para disub. ring); ^{1}H NMR (DMSO-d6): δ 8.92 (s, 1H, NH), 7.65-7.34 (m, 8H, Ar-H), 2.42 (s, 2H, CH_2); ^{13}C NMR (DMSO-d6): δ 169 (C=O), 142, 139, 135, 133, 127, 126, 122 (Ar-C), 43.2 (NCH_2CO); MS m/z : 263, 168, 154.

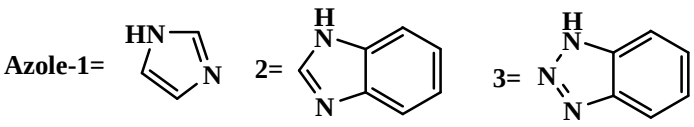
RESULTS AND DISCUSSION

The acylation of substituted aromatic primary amines like aniline, p-toluidine and p-chloroaniline in presence of TEA by chloroacetylchloride in toluene gave corresponding N-chloroacetyl arylamines in quantitative yields. Which were subjected to N-alkylation in second step with azoles like imidazole, benzimidazole and benzotriazole in acetone in presence of anhydrous K_2CO_3, the corresponding acetamides obtained in good yields. When aniline was acylated with chloroacetyl chloride gave 2-chloro-N-phenylacetamide which on alkylation with imidazole obtained **1a** in 74% yield. Which was characterized as 2-(1H-imidazol-1-yl)-N-phenylacetamide. The IR spectra of **1a**showed strong peak at 3236, 1647 cm^{-1}corresponding to NH and C=O groups. The two peak at 757 and 690 cm^{-1} are due to mono substituted phenyl ring. ^{1}H NMR spectrum of **1a** showed a singlet at 10.78 ppm due to NH proton of amide group. The multiplate observed at 7.65-7.00 ppm corresponds to the presence of aromatic protons of imidazole and phenyl ring .The isolated $–CH_2$ protons appear at 5.10 ppm as singlet. ^{13}C NMR displayed peaks in three distinct regions, the peak at 165 ppm is due to C=O of amide group, the aromatic carbons regions 139-117 ppm and at 40.23 for $–CH_2$ group of **1a**. The (M^+-1) peak in Mass spectra attributed to the loss of proton from amide group. Similar spectral data were seen for **2a** and **3a** except variation in aromatic multiplates with less number of proton in benzimidazole and benzotriazole. **1b**, **2b** and **3b** distinctly showed similar spectral data. While in **1c**, **2c** and **3c** due to presence of more electronegative Chlorine atom in aromatic ring the downfield values appears in ^{1}H and ^{13}C NMR spectrum(Scheme).



1a,b,c 2a,b,c 3a,b,c

R a =H, b= 4CH_3, c = 4Cl



Scheme: Synthesis of 2-(1H-azol-1-yl)-N-(substituted phenyl) acetamides

All the synthesized compounds were evaluated for their antibacterial and antifungal activity against *E. coli, S. aureus,*and *C. albicans, A. niger* respectively by Disc diffusion method (Well method, Disc size 6mm, Hi media) using nutrient agar. The compounds were tested at the concentration of 100µg/mL in DMF.

Table 1: Results of the antimicrobial activity of compounds 1a,b,c 2a,b,c and 3a,b,c.

Compound	Antimicrobial activity*			
	E. coli	***S. aureus***	***C. albicans***	***A. niger***
1a	8.44	-	7.11	-
1b	26.44	16.19	9.65	15.80
1c	20.92	29.12	23.90	11.13
2a	9.16	13.90	14.72	-
2b	9.49	12.89	8.64	-
2c	17.38	20.43	11.11	-
3a	12.19	10.20	9.30	14.07
3b	10.78	-	7.34	9.51
3c	11.71	8.06	8.11	10.23
Streptomycin	**18.22**	**20.12**	**NA**	**NA**
Amphotericin-B	**NA**	**NA**	**14.23**	**15.34**

**Zone of inhibition measured in mm, "-" means no zone of inhibition, NA-Not Applicable.*

CONCLUSION

The study reports the facile synthesis of azole acetamides by acylation-alkylation reaction steps. The methodology reported is clean, simple and efficient giving good yields of the reported compounds. In antimicrobial evaluation, imidazole acetamides were shown promising antimicrobial activities against both the strains.

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REFERENCES

[1]M. J.Madeleine, M. L.Kenneth,*Arkivoc*,**2010,** 8, 189-250.
[2] B. Narasimhan, D.Belasare, D. Pharande, V. Mourya, A. Dhake, *Eur. J. of Med. Chem.*, **2004**, 39,10, 827-834.
[3] A. Palani, S. Shapiro, J. W. Clader, W. J. Greenlee, S. Vice, *et.al.*,*Bioorg. Med. Chem. Lett.*, **2003**, 13, 4, 709-712.
[4]O.H. EI. N. Ahmed,A. A. R. Mohamed, S. T. Gaballah, *Arkivoc*,**2009**, 12, 119-130.
[5] N. Sati, S. Kumar, M. S. M. Rawat, *Ind. J. of Chem.*,**2012**, 51B, 318-322.
[6] T. C. Maria, C. Cenzo, O. Valentina, M. Micaela, C. Omar,*Eur. J. of Med.Chem.*, **2003**, 38, 5, 513-518.
[7] S. Nadeem, M. Shamsher-Alam, W. Ahsan,*Acta Pharma*, **2008**, 58, 445-454.
[8] B. M. Robert, R. Andre, L. L. Skaletzky, *J. of Med. Chem*., **1971**, 14, 10, 963-968.
[9] H. M. H. Abdel, A. M. GE. Mohamed, A. AM. EI. A. Abu-Bakr, M. O. Ismail, *Phos, Sulfur and Silicon and The Related Elements*, **2009**, 184, 9, 2263-2280.
[10]M. A. Salem, H. K. H. Thabet, M. H. Helal, A. S. Abdelaal, Y. A. Ammar,*Chem. Sciences J*.,**2011**, 32, 1-12.
[11] R. Kulandsamy,A. V. Adhikari, J. P. Stables, *Bull. of Kor. Chem. Soc*.,**2010**, 31, 11, 3318-3326.
[12] D. Martin, M. Miroslav, K. Jiri, K. Katarina, *Molecules*,**2002**, 7, 363-373.
[13]T. A. Naik, K. H. Chikhalia, *E-Journal of Chem*.,**2007**, 4, 1, 60-66.
[14] B. Danuta,B. Krzysztof, M. Agnieszka, Z. Krzysztof, P. Anna, R. Andrzej, *ActaBiochem.Polonica*,**1998**, 45, 1, 41-57.
[15] A. R. Katritzky, M. Wang, H. Yang, S. Zhang, N. G. Akhmedov, *Arkivoc*, **2002**, 8, 134-142.