

NEWER ROUTE FOR THE SYNTHESIS OF N-PYRAZOLYL CARBOXYL- SULFONAMIDES

Shivdas Bajod¹, Namdeo Chavhan¹, Vijaykumar Markad², Kisan Kodam², Jagrut Waghmare³ and
Sharad Shelke^{1*}

Research Center, Department of Chemistry, S.S.G.M. College, Kopergaon, Dist-Ahmednagar (MS) 423601, India¹.

Biochemistry Division, Department of Chemistry, University of Pune, Pune (MS) 411007, India².

Department of Chemistry, Jijamata Mahavidyalaya, Buldhana (MS) 443001, India².

* Corresponding author

Abstract: In this study the investigations on the synthesis of *N*-Acyl Sulfonamide derivatives of pyrazole nucleus are reported. Ethyl-3-pyrazole carboxylate **1** has been used as starting material and it treated with aryl boronic acid in cupric acetate and DMF as a solvent afford *N*-aryl ethyl-3-pyrazole carboxylate **2** followed by alkaline hydrolysis to get *N*-aryl ethyl-3-pyrazole carboxylic acid **3**. When compound **3** stirred with aryl sulfonylamide in the presence of DCC, DMAP in DCM affords *N*-pyrazolylcarboxylsulfonamides **4**.

Keywords: *N*-acylsulfonamide, Pyrazole, Boronic acid, DCC, DMAP.

I. INTRODUCTION

Nitrogen and sulfur containing compounds like sulfonamide is important biological compound. ¹ ²Sulfonamides have been associated with antibacterial, ³ anticancer, ^{4,5} and anti-proliferative ⁶ activities. Biphenyl derivatives of sulfonamides showed excellent angiotensin II receptor antagonist activity. ⁷ In the last decade, SAR study ^{8,9} of sulfonamoyl compounds has been reported by various researchers. It plays a key role in the field of organometallic chemistry. As an example sandwich cobalt and rhodium complex with combination of *N*-acyl sulfonamides is applied for lung cancer therapy. ¹⁰ *N*- α - β -unsaturated acyl sulfonamides shows addition properties to organometallic reagents. ¹¹

The literature survey revealed that *N*-acyl sulfonamide derivatives have been used for chemoselective *N*-acylation reagent. ¹² Recently, application of sulfonamide in asymmetric conjugated addition of Grignard reagents to α - β -unsaturated carboxylic acids have been investigated. ¹³

Due to the sulfonamides shows versatile bioactivity, researcher very much interested in their study of synthetic properties ¹⁴ and pay attention towards synthesis of their derivatives ¹⁵⁻¹⁷. Various methods for the synthesis of aryl and heterocycle derivatives of *N*-acyl sulfonamide ¹⁸⁻²⁰ have been reported in the literature.

Pyrazole derivatives also exhibited antibacterial, ²¹ antifungal ²² and anti-hyperglycemic ²³ activity. Pyrazole nucleus shows anti-HCV ²⁴ as well as HIV-1 protease inhibitors ²⁵ property. Due to diverse biological activity associated with pyrazole derivatives. Various researchers have been focusing on their synthesis. ²⁶⁻²⁷ Newer different routes for the synthesis of pyrazole nucleus has been reported in the literature. ²⁸⁻³⁰

Biological activity associated with *N*-acyl sulfonamide and in continuation of effort in the study of bioactive heterocycles, ³¹⁻³⁴ we promoted us to synthesis of *N*-pyrazolylcarboxylsulfonamides and their biological evaluation.

International Journal of Innovative Research in Science, Engineering and Technology

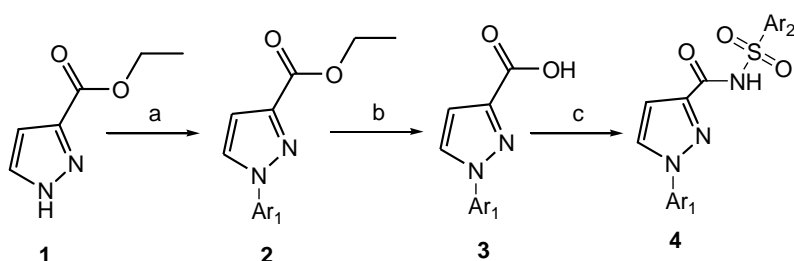
(An ISO 3297: 2007 Certified Organization)

Vol. 2, Issue 12, December 2013

II. RESULT AND DISCUSSION

In present investigation the synthetic approach was achieved in three steps as shown in Scheme-1. Initially commercially available ethyl-3-pyrazolecarboxylate **1** has been treated with aryl boronic acid with copper acetate afforded N-aryl ethyl-3-pyrazolecarboxylate **2**. Compound **2**, when subjected to alkaline hydrolysis gave corresponding acid **3**, followed by treatment with aryl sulfonamide in presence of DMAP and DCC afforded N-pyrazolylcarboxasulfonamides **4** (Scheme-I).

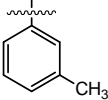
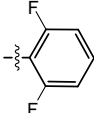
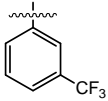

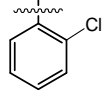
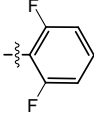
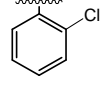

SCHEME-I



Scheme-I: a) $\text{Ar}_1\text{B}(\text{OH})_2$, 2.1 equiv., $\text{Cu}(\text{OAc})_2$, 1.5 equiv., Pyridine, 2 equiv., 4A Mol. Sieve, DMF, RT, 18h; b) aq. NaOH, EtOH, H^+ ; c) $\text{Ar}_2\text{SO}_2\text{NH}_2$, 2 equiv., DCC, 1 equiv., DMAP, 1 equiv., DCM, RT, 18h.

In each step, progress of the reaction was monitored by TLC (Thin layer chromatography). Formation of the intermediate compound **2** was confirmed by TLC as well as M.P. and mixed M.P. Formation of acid **3** was confirmed by routine sodium bicarbonate test, TLC and M.P. and LCMS. Characterization data of synthesized compound has been summarized in **Table 1**.

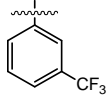
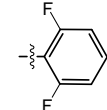
TABLE 1. CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS **4a-4e**.

Entry	Ar_1	Ar_2	Mp ($^{\circ}\text{C}$)	Yield (%)
4a			198	79.06
4b			190	81.10
4c			200	80.50
4d			192	82.11

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 2, Issue 12, December 2013

4e			210	81.22
----	---	---	-----	-------

*The Melting Point was taken in M. P. apparatus Model: KI-11 (MP-D), Make: Kumar Sales Corporation, Mumbai (India).

The structure of the titled compounds 4a-4e was confirmed by spectral studies such as IR, ¹HNMR, LCMS.

III. EXPERIMENTAL

All the recorded melting points were determined on M. P. apparatus Model: KI-11 (MP-D), Make: Kumar Sales Corporation, Mumbai (India) and are uncorrected. FTIR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr pellets. The NMR spectra were recorded on a Bruker 400 MHz instrument using CDCl₃ (deuterated chloroform) as a solvent and TMS (tetramethylsilane) as an internal standard; the chemical shifts (δ) are reported in ppm (part(s) per million) and coupling constants (J) are given in Hertz. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), dd (double doublet), and m (multiplet). Mass spectra were recorded on a Finnigan mass spectrometer. TLC was performed on pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany)

Synthesis of *N*-Pyrazolylcarboxasulfonamides 4a-4e

A solution of *N*-aryl 1*H*-pyrazole-3-carboxylic acid **3** (1 equiv.) and aryl sulfonamide (2 equiv.) in 10 mL of DCM (dichloromethane) was added drop wise, at R.T., to a stirred solution containing DCC (1 equiv.) and DMAP (1 equiv.). The reaction mixture was stirred at R.T. for 18 hrs. The progress of the reaction was monitored by TLC (Thin layer Chromatography). After completion of the reaction, the mixture was extracted with DCM, washed with 10 % aqueous NaHCO₃ and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the crude residue was purified by column chromatography (20% ethyl acetate/n-hexane) to afford titled compound **4a-4e**.

This typical experimental procedure was followed to prepare other analogues of this series. The compounds synthesized by above procedures have been listed in **Table 1** with their characterization data.

4a: IR (KBr) ν/cm^{-1} : 3243 (-NH), 1709 (-C=O), 1606 (C=N), 765 (C-F); ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 2.47 (s, 3H, CH₃) 6.97-7.92 (m, 9H, HAr), 9.68 (s, 1H, NH); MS (m/z): 378 (M⁺+1).

4b: IR (KBr) ν/cm^{-1} : 3248 (-NH), 2948 (-CH₃), 1705 (-C=O), 1660 (C=N), 757 (C-Cl); ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 6.79-8.39 (m, 10H, HAr), 9.60 (s, 1H, NH); MS (m/z): 428 (M⁺+1).

4c: IR (KBr) ν/cm^{-1} : 3242 (-NH), 1709 (-C=O), 1663 (C=N), 760 (C-Cl); ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 6.63-7.87 (m, 9H, HAr), 9.63 (s, 1H, NH); MS (m/z): 398 (M⁺+1).

4d: IR (KBr) ν/cm^{-1} : 3250 (-NH), 1710 (-C=O), 1661 (C=N), 760 (C-Cl); ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 6.93-8.34 (m, 10H, HAr), 9.52 (s, 1H, NH); MS (m/z): 445.9 (M⁺+1).

4e: IR (KBr) ν/cm^{-1} : 3198 (-NH), 1715 (-C=O), 1671 (C=N), 765 (C-F); ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 7.03-8.00 (m, 9H, HAr), 9.65 (s, 1H, NH); MS (m/z): 431.8 (M⁺+1).

IV. CONCLUSION

In conclusion, various carboxasulfonamides **4** having pyrazole nucleus were synthesized successfully by newer route. It was found that yield of titled compound is good.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 2, Issue 12, December 2013

ACKNOWLEDGMENT

The authors are thankful to the Director of SAIF, Punjab University (Chandigarh, India) for the spectral analysis. We are also grateful to the Principal Dr. K. H. Shinde and Dr. A. B. Nikumbh, (HOD), S.S.G.M. College, Kopargaon, Ahmednagar (MH) for providing research facilities and constant encouragement.

REFERENCES

- [1] M. G. Banwell, C. F. Crasto, C. J. Easton, A. K. Forrest, T. Karoli, D. R. March, L. Mensah, M. R. Nairn, P. J. O'Hanlon, M. D. Oldham, and W. Yue, "Analogues of SB-203207 as Inhibitors of tRNASynthetases," *Bioorg. Med. Chem. Lett.*, Vol.10, pp. 2263-2266, 2000.
- [2] H. Juteau, Y. Gareau, M. Labelle, C. F. Sturino, N. Sawyer, N. Tremblay, S. Lamontagne, M. Carrière, D. Denis, and K. M. Metters, "Structure-Activity Relationship of Cinnamic Acylsulfonamide Analogues on the Human EP₃ Prostanoid Receptor," *Bioorg. Med. Chem.*, Vol.9, pp. 1977-1984, 2001.
- [3] G. H. Miller, P. H. Doukas, and J. K. Seydel, "Inhibition of Folate Synthesis with Antibacterial Activity and Physicochemical Parameters," *J. Med. Chem.*, Vol. 15 (7), pp. 701-706, 1972.
- [4] M. Lopez, L. F. Bornaghi, A. Innocenti, D. Vullo, S. A. Charman, C. T. Supuran, and S. A. Poulsen, "Sulfonamide Linked Neoglycoconjugates-A New Class of Inhibitors for Cancer-Associated Carbonic Anhydrases," *J. Med. Chem.*, Vol. 53 (7), pp. 2913-2926, 2010.
- [5] R. Mohan, M. Banerjee, A. Ray, T. Manna, L. Wilson, T. Owa, B. Bhattacharyya, and D. Panda, "Antimitotic Sulfonamides Inhibit Microtubule Assembly Dynamics and Cancer Cell Proliferation," *Biochem.*, Vol. 45, pp. 5440-5449, 2006.
- [6] H. Li, J. Yang, S. Ma, and C. Qiao, "Structure-based design of rhodanine-based acylsulfonamide derivatives as antagonists of the anti-apoptotic Bcl-1 protein," *Bioorg. Med. Chem.*, Vol.10, pp. 4194-4200, 2012.
- [7] L. L. Chang, W. T. Ashton, K. L. Flanagan, T. Chen, S. S. O'Malley, G. J. Zingaro, P. K. S. Siegl, S. D. Kivlighn, V. J. Lotti, R. S. L. Chang, and W. J. Greenlee, "Triazolinone Biphenylsulfonamides as Angiotensin II Receptor Antagonists with High Affinity for Both the AT₁ and AT₂ Subtypes," *J. Med. Chem.*, Vol.37, pp. 4464-4478, 1994.
- [8] K. Song, M. J. Kim, H. J. Seo, S. Lee, M. E. Jung, S. Kim, J. Kim, and J. Lee, "Synthesis and structure-activity relationship of novel diarylpyrazole imide analogues as CB₁ cannabinoid receptor ligands," *Bioorg. Med. Chem.*, Vol. 17, 3080-3092, 2009.
- [9] J. H. Musser, A. F. Kreft, R. H. Bender, D. M. Kubrak, D. Grimes, Carlson, R. P. James, M. Hand, and J. Chang, "N-[(Arylmethoxy) phenyl] Carboxylic Acids, Hydroxamic Acids, Tetrazoles, and Sulfonyl Carbamides. Potent Orally Active Leukotriene D₄ Antagonists of Novel Structure," *J. Med. Chem.*, Vol.33, pp. 240-245, 1990.
- [10] H. Dou, W. Zhong, L. Yang, T. Wang, H. Yan, and Y. Hou, "Synthesis, cytotoxic activities and cell cycle arrest profiles of half-sandwich N-sulfonamide based dithio-o-carborane metal complexes," *Bioorg. Med. Chem.*, Vol. 20, pp. 4693-4700, 2012.
- [11] H. Nagashima, N. Ozaki, M. Washiyama, and K. Itoh, "Conjugate Addition of Organocopper Reagents to N-Tosylated α - β -Unsaturated Amides," *Tetrahed. Lett.*, Vol. 26 (5), 657-660, 1985.
- [12] K. Kondo, E. Sekimoto, J. Nakao, and Y. Murakami, "Conjugate Addition of Organocopper Reagents to N-Tosylated C α , B-Unsaturated Amides," *Tetrahed.*, Vol. 56, pp. 5843-5856, 2000.
- [13] U. Chiacchio, A. Corsaro, G. Gambra, A. Rescifina, A. Piperno, R. Romeo, and G. Romeo, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Tetrahed.: Asymm.*, Vol. 2002, 13, pp. 1915-1921.
- [14] M. Zhu, K. Fujita, and R. Yamaguchi, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Org. Lett.*, Vol. 2010, 12(6), pp. 1336-1339.
- [15] S. Hajra, B. Maji, and A. Karmakar, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Tetrahed. Lett.*, Vol. 46, pp. 8599-8603, 2005.
- [16] P. Dauban, and R. H. Dodd, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Org. Lett.*, Vol. 2(15), pp. 2327-2329, 2000.
- [17] H. S. Knowles, A. F. Parsons, R. M. Pettifer, and S. Rickling, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Tetrahed.*, Vol. 56, pp. 979-988, 2000.
- [18] A. R. Katritzky, S. Hoffmann, and K. Suzuki, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *ARKIVOC*, Vol. (xii), 14-22, 2004.
- [19] N. Ishizuka, K. Matsumura, K. Hayashi, K. Sakai, and T. Yamamori, "Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents," *Synthe.*, Vol. 6, pp. 784-788, 2000.
- [20] G. M. Blackburn, and H. Turkmen, "Synthesis of α -fluoro- and α,α -difluoro-benzenemethanesulfonamides: new inhibitors of carbonic anhydrase," *Org. Biomol. Chem.*, Vol. 3, pp. 225-226, 2005.
- [21] A. Tanitame, Y. Oyama, K. Ofuji, M. Fujimoto, N. Iwai, J. Hiyama, K. Suzuki, H. Ito, H. Terauchi, M. Kawasaki, K. Nagai, M. Wachi, and J. Yamagishi, "Synthesis and antibacterial Activity of a Novel Series of Potent DNA Gyrase Inhibitors. Pyrazole Derivatives," *J. Med. Chem.*, Vol. 47 (14), pp. 3693-3696, 2004.
- [22] B. K. Karale, V. P. Chavan, A. S. Mane, R. V. Hangarge, C. H. Gill, and M. S. Shingare, "Synthesis, Characterization and Antimicrobial Activities of Some 2-(1,3-Diphenyl-1H-pyrazole-4-yl)-3-chlorochromones and 2-(1,3-Diphenyl-1H-pyrazole-4-yl)-4-(2-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepines," *Korean J. Med. Chem.*, Vol. 10 (2), pp. 84-91, 2000.
- [23] A. Sharon, R. Pratap, P. Tiwari, A. Srivastava, P. R. Maulik, and V. J. Ram, "Synthesis and in vivo antihyperglycemic activity of 5-(1H-pyrazole-3-yl)methyl-1H-tetrazole," *Bioorg. Med. Chem. Lett.*, Vol. 15 (8), pp. 2115-2117, 2005.
- [24] A. F. Sherif, Rostoma, A. S. Manal, and A. E. Euro, "Polysubstituted pyrazoles, part 5¹ Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogues and some derived ring systems. A novel class of potential antitumor and anti-HCV agents," *J. Med. Chem.*, Vol., 38, pp. 959-974, 2003.
- [25] P. W. Baures, "Heterocyclic HIV-1 Protease Inhibitors," *Org. Lett.*, Vol. 1 (2), 249-252, 1999.
- [26] M. A. P. Martins, D. Emmerich, P. Beck, W. Cunico, C. M. P. Pereira, A. P. Sinhorin, S. Brondani, R. Peres, M. V. M. Teixeira, H. G. Bonacorso, and N. Zanatta, "One-Pot Synthesis of Pyrazole-5(3)-carboxamides," *Synth. Comm.*, Vol. 34 (10), pp. 1915-1923, 2004.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 2, Issue 12, December 2013

- [27] E. A. Aly, M. A. El-Borai, and M. A. Barren, "A convenient synthesis of some novel pyrazole derivatives," *Indian J. Chem.*, Vol. 43B, pp. 1355-1359, 2004.
- [28] F. Palacios, A. M. Ochoa, D. Retana, and J. Pagalday, "A Regioselective Synthesis of 5-Pyrazolones and Pyrazoles from Phosphazenes derived from Hydrazines and Acetylenic Esters," *Tetrahed.*, Vol. 55 (50), pp. 14451-14458, 1999.
- [29] D. Bourissou, and G. Bertrand, "Effect of lithiation on the reactivity of diazo derivatives with sulfonylalkynes: application to the synthesis of three isomeric trisubstituted pyrazoles," *Tetrahed. lett.*, Vol. 40 (5), pp. 883-886, 1999.
- [30] X. L. Ren, H. B. Li, C. Wu, and H. Z. Yang, "Synthesis of a small library containing substituted pyrazoles," *ARKIVOC*, Vol. (xv), pp. 59-67, 2005.
- [31] S. Shelke, G. Mhaske, S. Gadakh, and C. Gill, "Green synthesis and biological evaluation of some novel azoles as antimicrobial agents," *Bioorg. Med. Chem. Lett.*, Vol. 20, pp. 7200-7204, 2010.
- [32] S. Shelke, N. Salunkhe, R. Jadhav, and B. Karale, "Synthesis and Antimicrobial Screening of Some Fluorinated Azoles Containing (2-(6-Methyl-2-P-Tolyl-1H-Imidazo[1,2-a]Pyridin-3-yl) Nucleus," *J. Korean Chem. Soc.*, Vol. 54 (1), pp. 59-64, 2010.
- [33] S. N. Shelke, N. R. Dalvi, B. K. Kale, M. S. More, C. G. Gill, and B. K. Karale, "Synthesis and Antimicrobial Screening of Some Fluorinated Azoles Containing (2-(6-Methyl-2-P-Tolyl-1H-Imidazo[1,2-a]Pyridin-3-yl) Nucleus," *Indian J. Chem.*, Vol. 46B, pp. 1174-1177, 2007.
- [34] N. R. Dalvi, S. N. Shelke, B. K. Karale, and C. H. Gill, "Synthesis of 1-(2-Hydroxy-phenyl)-3-piperidin-1-yl-propenone by Ultrasonic Irradiation," *Synth. Commun.*, Vol. 37, pp. 1421-1424, 2007.

BIOGRAPHY



Dr. Sharad N. Shelke received his Ph.D. degree in Chemistry in 2007 from Research Centre, Department of Chemistry, Rayat Shikshan Sanstha's, S.S.G.M. College, Kopargaon, Dist: Ahmednagar (MS), India (Recognized Research Centre, Affiliated to University of Pune), under the supervision of Prof. C. H. Gill. Presently, he is working at S.S.G.M. College, Kopargaon as an Assistant Professor. He has investigated various bioactive heterocycles and green method, which is applicable in organic synthesis. In 2005, he received the "Teacher Fellowship" from UGC. He has completed number of projects received from various funding agencies. His research interests are investigation of bioactive heterocyclic compound and designation of green chemical reactions and their applications in organic synthesis. He has published over 20, scientific articles, including research articles and patent.