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Solvent Effects on the [3+2] Cycloaddition of 2-Furfural Oxime and Ethyl Propiolate: Unexpected Change in Regioselectivity

Promi Rahman[1], Amy Glanzer[1], Jaffarguriqbal Singh[1], Nanette M. Wachter[1], Jonathan Rhoad[2], Richard W. Denton[3,*]

[1]Department of Chemistry, Hofstra University, Hempstead, United States of America
[2]Department of Chemistry, Missouri Western State University, St. Joseph, United States of America
[3]Department of Chemistry, Barnard College, New York, United States of America
*Corresponding author: rdenton@barnard.edu

Abstract The effect of solvents on the 1,3-dipolar cyclization reaction between ethyl propiolate and 2-furfuryl nitrile oxide was studied in various organic solvents. As expected, the major product was ethyl-3-(2-furanyl)-5-carboxylate. The relative ratio of the 3,5- to 3,4- disubstituted isoxazoles in dichloromethane, toluene, ethanol and dimethyl sulfoxide were 3.4, 2.0, 1.9 and 1.5 respectively. Experimental regioselectivity was found to be dissimilar to density functional theory predictions.

Keywords: *1,3-Dipolar cyclization, isoxazole, solvent effect, regioselectivity, density functional theory calculations*

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1. Introduction

Isoxazoles possess a wide range of biological properties including antitumor, antifungal, antibiotics, antimalarial, antituberculosis and herbicidal activities [1,2,3,4]. Classic examples include the mefloquine-isoxazole carboxylic ester **1** [1], the penicillin-resistant antibiotics oxacillin (**2**) [4], and the histone deacetylase (HDC) inhibitor **3** [3].

While 3,5-disubstituted isoxazoles are well-documented for their medicinal properties and as synthetic precursors [3,4,5,7], their 3,4-disubstituted counterparts are less prevalent. Notwithstanding, the latter also exhibits significant biological activities and are key starting materials for some natural products. Examples within this class of compounds include the tetrahydroindazole-isoxazole (**4**), a mild inhibitor of *Myco-bacterium Tuberculosis* [9], compound **5** (a voltage-gated sodium (NaV1.8) channel modulator) and the carboxamide carboxylic isoxazole **6**, a growth inhibitor of some phytopathogenic fungi [10]. Other examples include key precursors for the biologically active natural product trachyspic acid [11]. Compounds **7** and **8** were side products prepared in an attempt to construct the perhydrophenanthrene system of the anti-inflammatory triterpenoid, celastrol [12], (Figure 1).

Several methods are used to prepare isoxazoles, including the reaction of hydroxylamine with α,β - unsaturated carbonyl compounds [13,14] and the intermolecular [3+2] cycloaddition of alkynes and nitrile oxides [15,16].

The latter is efficient, convergent and among the more popular methods. Previous studies reveal that this type of regioselectivity favors the 3,5- to the 3,4-disubstituted adduct [13,15,16]. Molecular orbital calculations highlighted that a more favorable overlap of the HOMO of the dipolarophile and the LUMO of the dipole aligned with the selectivity observed experimentally [18,19].

Sharpless and coworkers synthesized these isoxazoles using copper as catalyst. Under these reaction conditions the 3,5-isomer were prepared selectively and with high yields [20]. Other groups have capitalized on their results and applied this method of synthesis to their research [21].

The synthesis of the 3,4-disubstituted isoxazole adduct is hardly reported in the literature [9,16,22]. The most recent citation by Chalyk and coworkers. exploited the 1,3-dipolar cycloaddition reaction between in situ generated nitrile oxides and enamines to generate 3,4-disubstituted isoxazole products [16]. Using hybrid density functional theory (DFT) calculations, the Houk's group predicted and explained that the regioselectivity for the unfavored 3,4-isomer in the cycloaddition reaction between mesitonitrile oxide and the methyl propiolate should increase in non-polar solvents [19]. This regioselectivity was due to the lesser polar character of the 3,4-disubstutued isoxazole transition state in comparison to that of the 3,5 –disubstituted one.

Herein, we report the effect of solvent on the regioselectivity of the uncatalyzed [3+2] cycloaddition reaction between the in situ generated 2-furfuryl nitrile oxide **10** and ethyl propiolate **11**. DFT calculations revealed an unexpected disparity between theory and experimental regioselectivity.

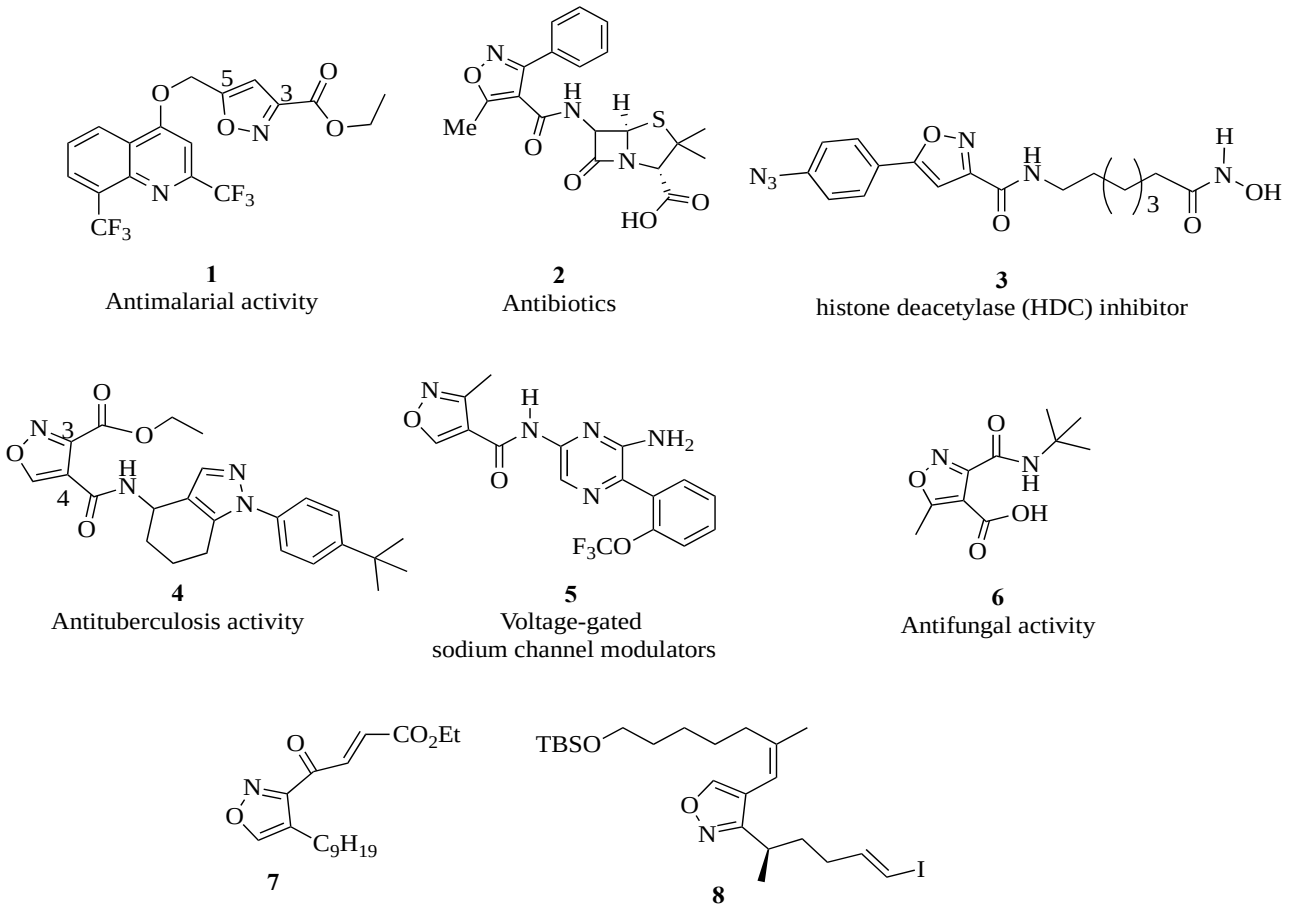


Figure 1. Some important 3,5- and 3,4-disubstituted isoxazoles

2. Materials and Methods

2.1. Chemistry

Ethyl propiolate **11** was reacted with nitrile oxide **10**, which was generated in situ from furfural oxime **9** [23] and sodium hypochlorite (NaOCl), (Scheme 1).

2.2. Experimental Section

All isoxazoles were synthesized by following the general procedure given for selected solvents. The compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR spectral data. The ratio of the regioisomers was determined by comparing the integrals of the methine protons for the isoxazole mixture in the crude products. A Perkin Elmer Spectrum BX FT IR system. A JEOL ECS 400 MHz FT-NMR spectrometer with TMS was used as internal standard for recording the ^{1}H and ^{13}C NMR spectra of the compounds in deuterated chloroform-*d* ($CDCl_3$). Thin Layer Chromatograpy (TLC) was done to analyze reaction using pre-coated silica gel plates. These were viewed under UV light at 254 nm and developed using potassium permanganate stain solution.

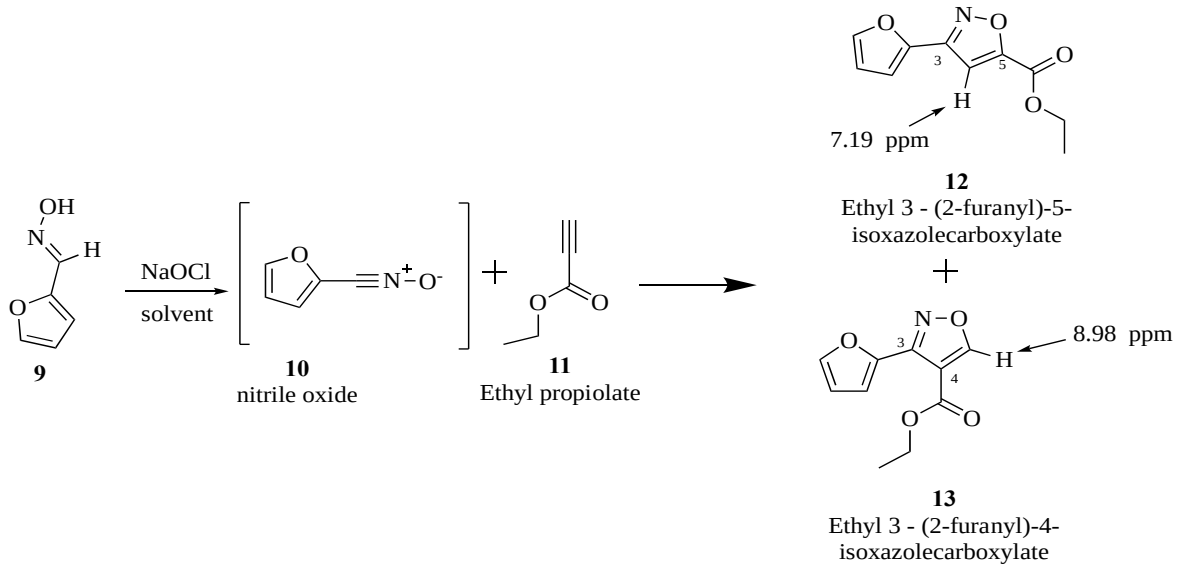
2.2.1. General Procedure for the Synthesis Isoxazoles

To a mixture of ethyl propiolate, **11** (0.32 g, 3.27 mmoles), furfural oxime, **9** (0.20 g, 1.80 mmoles) and **solvent** (5 mL) in a 100 mL round bottom flask was added bleach (0.354 M NaOCl, 13.8 mL, 4.88 mmoles) and the reaction mixture was stirred overnight at room temperature. The reaction was extracted with dichloromethane (3 x 10 mL) and the combined organic layer was washed with water (2 x 10 mL) and brine (10 mL), then dried with anhydrous Na_2SO_4. The mixture was filtered and concentrated by rotary evaportion. The crude product was then examined using proton NMR to identify the ratio of the **12/13** formed in the reaction. In some cases, flash column chromatography of the cude product produced the isoxazole products as a yellow oil.

Ethyl 3-(2-furanyl)-5-isoxazolecarboxylate (12) and Ethyl 3-(2-furanyl)-4-isoxazole carboxylate (13)
Reaction in dichloromethane:

Sample data for reaction ran in dichloromethane: yield (85.7 mg, 23%), ratio of **12**/**13** is 1:3, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 0.23 H), 7.63 (d, J = 3.6 Hz, 0.23 H). 7.61 - 7.58 (m, 1 H), 7.19 (s, 0.77 H), 6.99 (d, J = 3.6 Hz, 0.77 H), 6.58 – 6.55 (m, 1 H), 4.46 (q, J = 6.8 Hz, 1.54 H), 4.37 (q, J = 6.8 Hz, 0.46 H), 1.44 (t, J = 7.3 Hz, 2.31 H), 1.40 (t, J = 7.0 Hz, 0.69 H).

^{13} C NMR (100 MHz, $CDCl_3$) δ = 14.3, 14.4, 61.5, 62.6, 107.0, 111.3, 111.9, 112.1. 116.4, 143.3, 144.6, 144.8, 155.5. 156.7, 160.8, 164.3. IR (cm^{-1}) *v* = 3131, 2983, 1739, 1617, 1582, 1505, 1517.



Scheme 1. Synthesis of 3,5- and 3,4-disubstitued isoxazole products 12 and 13

3. Results and Discussion

Different solvents provided varying ratios of the 3,4- and the 3,5-disubstituted isoxazoles (**12** and **13**) in very low yields after column purification (Table 1). Careful analysis of the ^{1}H NMR spectrum indicated that the methine proton on the isoxazole rings of each product after workup is distinct. These singlets resonated at 7.19 ppm and 8.98 ppm for compounds **12** and **13** respectively. The product ratios were determined from the integrations of these resonances. Although the 3,5-disubstituted product was always favored, the ratio of **12/13** decreased from 3.4 to 1.5 as the solvent polarity increased. (Table 1).

Table 1. The effect of solvent polarity on the ratio of the 1,3-cycloaddition products 12 and 13

Solvent	Dielectric Constant [24]	Ratio of **12** /**13*** **(% isolated yield)**
Dichloromethane	8.9	3.4 (**23**)
Toluene	2.4	2.0**
Ethanol	25	1.9**
Dimethyl sulfoxide	47	1.5 (**8**)

* Ratio determined from the H^1-NMR of the crude mixture of compounds **12** and **13** after work up of experiment.
** Product was not isolated.

3.1. Theoretical Calculations

To rationalize the decrease in selectivity for **12**, the transition states **TS-3,5** and **TS-3,4** were optimized in the gas phase, DMSO and dichloromethane using the Gaussian 09 [25] at the B3LYP/6-31+G(d) [26,27,28,29,30] level of theory.

These transition states were shown to be single-order saddle points each with one imaginary frequency. The imaginary vibrational frequencies correlated with the direction of the formation of the two sigma bonds. (C3-C4) and (C5-O1).

Our calculations revealed that in the gas phase the 1,3-dipolar cyclization favors the formation of 3,4 disubstituted product **13** both kinetically and thermodynamically by 0.22 kcal/mol and 1.09 kcal/mol, respectively (Table 2). This result was expected as the interaction between the LUMO of the electron-deficient **11** and the HOMO of **10** is more favorable [18].

Table 2. The B3LYP/6-31G+(d) relative energies (ΔE_a/ kcal/mol) and dipole moment change (ΔD) of the transition states (TS-3,5 & TS-3,4) and products (12 & 13) in the gas phase, DMSO and dichloromethane

		E_{rel} (kcal/mol)[a]		D[b]
Product (Condition)	**Starting Material**	**Transition States**	**Product**	**TS-3,4/TS-3,5**
12(Gas)	0	13.08	- 78.95	-1.5
13 (Gas)	0	12.86	- 80.04	-2.7
12(DMSO)	0	14.34	-76.90	0.79
13(DMSO)	0	15.31	-76.77	-0.72
12(CH_2Cl_2)	0	15.13	-77.11	0.43
13(CH_2Cl_2)	0	14.31	-77.05	-1.02

a. Relative to reactants
b. D = dipole moment (TS) – Sum of dipole moments (reactants) [31].

Our results predicted that in dichloromethane **TS-3,4** was also favored kinetically by 0.82 kcal/mol but in DMSO, this stability was reversed, and **TS-3,5** was more stable by 0.97 kcal/mol. This neglibable effect of solvent on the difference in activation energy is no surprise, as these values are generally small and in our case less than 1 kcal/mol. A similar trend was reported in the literature by Mekelleche and coworkers [31].

Our results were quite similar to Houk's. predictions for the most part [19]. In his hands, the 1,3-dipolar cycloaddition reaction between mesitonitrile oxide and methyl propiolate favored the more polar 3,5-transition state to that of the less polar 3,4-transition state by 0.60 kcal/mol in CCl_4 and 5.6 kcal/mol in water). This stability was reversed in the gas phase by 1.3 kcal/mol. Thus an increase in solvent polarity was should favor the synthesis of the 3,5-disubstituted product and decreased the formation of the less polar 3,4- disubstituted isoxazole.

It should be noted that no experimental data was gathered at the time and these predictions were contingent on the relative dipole moments between the reactants and the transition states.

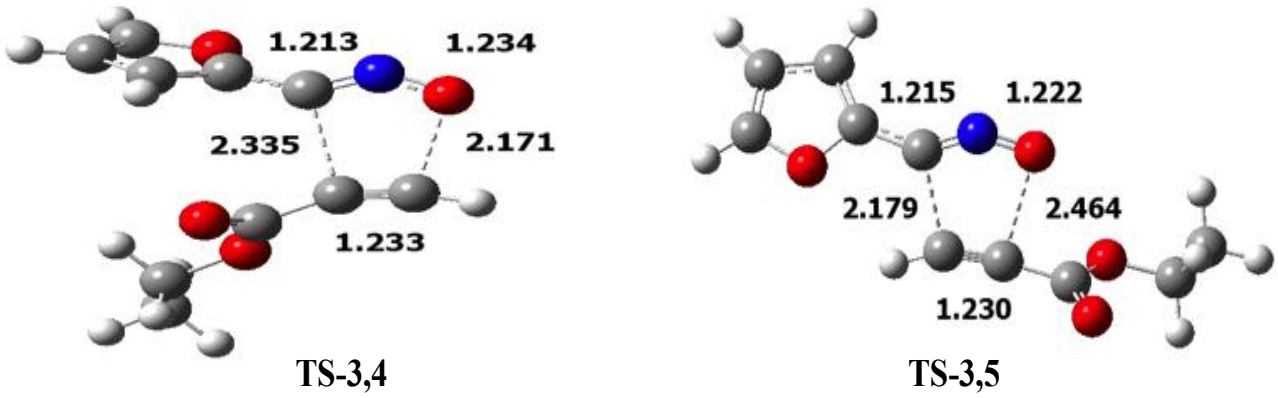


Figure 2. The optimized transitions states of the 3,4- and 3,5- disubstituted isoxazoles generated from B3LYP/6-31G+(d) calculations in the gas phase

In Mekelleche's report, the transition states of 1,3-dipolar reactions when less polar than those of the reactants, may be poorly stabilized in polar solvents [31].

In the reaction between ethyl propiolate **11** and furfural oxime **9**, the difference in dipole moments values between the transition states and the starting material were mostly negative except for **TS-3,5** in DMSO and dichloromethane which were less than one (0.79 and 0.43 respectively) (Table 2). Thus it is possible that more polar solvent could disfavor the formation of the more polar **TS-3,5** to that of the less polar **TS-3,4** [31]. This could account for the unexpected decrease in regioselectivity for the 3,5-disubstituted isoxazole **12** with increase in solvent polarity. Such computational result correlated well with the experimental result of roughly a 50-50 mixture in DMSO.

This conflict between experiment and theory may also imply that additional interactions may exist between the solvent (especially in DMSO) and the transition states that were not accounted for in the calculations provided. Hence, we are considering more robust calculations to further elucidate the cause of this unexpected experimental regioselectivity.

4. Conclusion

The effect of solvent polarity on the uncatalyzed 1,3-dipolar cycloaddition of ethyl propiolate and furfural oxime was studied both experimentally and using DFT calculations. The difference in the dipole moments of the reactants and the transition states were mostly negative. Thus pointing to the fact that the more polar transition state **TS-3,5** which led to the major regioisomers **13** might have been destabilized with increase in solvent polarity thus disfavoring the formation of the 3,5-disubstituted isoxazole **(12)** and unexpectedly improving the 3,4-disubstituted isoxazole **13**.

This project is pertinent to the synthesis of antibiotics such as oxacillin and its derivatives.

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References

[1] Mao, J: Yuan H., Wang, Y, Wan, B., Pieroni, M, Huang, Q, van Breemen, R. B., Kozikowski, A. P. and Franzblau, S.G., From serendipity to rational antituberculosis drug discovery of mefloquine-isoxazole carboxylic acid esters, *J. Med. Chem.*, 52 (22), 6966-7978, 2009.

[2] Kohl, M., Thunus, L. and Lejeune, R., Synthesis of 17β-Hydroxy Esters of 4-Estren-17β-ol-3-one and Carbenicillin, Ticarcillin, or Functionalized Oxacillin: Potentially Useful Conjugates for β-Lactamase-Based Homogeneous Immunoassays, *Bioconjugate Chem.*, 8 (5), 772-779, 1997.

[3] Neelarapu, R., Holzle, D. L., Velaparthi, S., Bai, H., Brunsteiner, M., Blond, S. Y. and Petukhov, P. A., Design, synthesis, docking, and biological evaluation of novel diazide-containing isoxazole- and pyrazole-based histone deacetylase probes. *J. Med. Chem.*, 54 (13), 4350-4364, 2011.

[4] Dong, K., Qin, H., Bao, X., Liu, F. and Zhu, C., Oxime-Mediated Facile Access to 5-Methylisoxazoles and Applications in the Synthesis of Valdecoxib and Oxacillin. *Organic Lett.*, 16 (20), 5266-5268, 2014.

[5] Harris, P. A., King, B. W., Bandyopadhyay, D., Berger, S. B., Campobasso, N., Capriotti, C. A. and Grady, L. C., DNA-encoded library screening identifies benzo [b][1, 4] oxazepin-4-ones as highly potent and monoselective receptor interacting protein 1 kinase inhibitors *J. Med. Chem.*, 59 (5), 2163-2178, 2016.

[6] Kalwat, M. A., Huang, Z., Wichaidit, C., McGlynn, K., Earnest, V., Savoia, C., Dioum, E. M., Schneider, J. W., Michele R. and Cobb, M. H. Isoxazole Alters Metabolites and Gene Expression, Decreasing Proliferation and Promoting a Neuroendocrine Phenotype in β-Cells, *ACS Chem. Bio.*, 11 (4), 1128-1136, 2016.

[7] Manning, J. R. and Davies, H. M. One-pot synthesis of highly functionalized pyridines via a rhodium carbenoid induced ring expansion of isoxazoles. *J. Am. Chem.*, 130 (27), 8602-8603, 2008.

[8] Caplan, J. F., Zheng, R., Blanchard, J. S. and Vederas, J C., Vinylogous amide analogues of diaminopimelic acid (DAP) as inhibitors of enzymes involved in bacterial lysine biosynthesis *Organic lett.*, 2 (24), 3857-3860, 2000.

[9] Guo, S., Song, Y., Huang, Q., Yuan, H., Wan, B., Wang,Y., He, R., Beconi, M. G., Franzblau, S. G. and Kozikowski, A. P., Identification, synthesis, and pharmacological evaluation of tetrahydroindazole based ligands as novel antituberculosis agents *J. Med. Chem.*, 53(2), 649-659, 2010.

[10] Vicentini C. B., Romagnoli, C., Andreotti, E. and Mares, D., Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi. *Journal of agricultural and food chemistry, J. Agric. Food Chem.*, 55(25), 10331-10338, 2007.

[11] Schmitt, D. C., Lam, L. and Johnson, J. S. Three-component coupling approach to trachyspic acid. *Organic Lett.*, 13 (19), 5136-5139, 2011.

[12] Kaiser, T. M., Huang, J. and Yang, J., Regiochemistry discoveries in the use of isoxazole as a handle for the rapid construction of an all-carbon macrocyclic precursor in the synthetic studies of celastrol *J. Org. Chem.*, 78 (12), 6297-6302, 2103.

[13] Pei, Y. and Wickham, B. O. Regioselective syntheses of 3-aminomethyl-5-substituted isoxazoles: A facile and chemoselective reduction of azide to amine by sodium borohydride using 1, 3-propanedithiol as a catalyst. *Tetrahedron Lett.*, 34 (47), 7509-7512, 1993.

[14] Csimbók, E., Takács, D., Balog, J. A., Egyed, O., May-Nagy, N. V. and Keserű, G. M. The first synthesis of isoxazolo [3, 4-c] pyridine-7-ones. *Tetrahedron Lett.*, 57 (39), 4401-4404, 2016.

[15] Rao, S. P., Kurumurthy, C., Veeraswamy, B., Poornachandra, Y., Ganesh K. C. and Narsaiah, B. Synthesis of novel 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives and their cytotoxic activity *Bioorg. Med. Chem, Lett.*, 24 (5), 1349-1351. 2014.

[16] Chalyk, B. A., Kandaurova, I. Y., Hrebeniuk, K. V. , Manoilenko, O. V. , Kulik, I. B., Iminov, R. T., Kubyshkin, V., Tverdokhlebov, A. V., Ablialimov, O. K. and Mykhailiuk, P. K., A base promoted multigram synthesis of aminoisoxazoles: valuable building blocks for drug discovery and peptidomimetics, *RSC Adv.*, 6 (31), 25713-25723, 2016.

[17] Kankala, S., Kankala, R. K., Gundepaka, P., Thota, N., Nerella, S., Gangula, M. R., Guguloth, H.,Kagga, M., Vadde, R. and Vasam, C. S., Regioselective synthesis of isoxazole–mercaptobenzimidazole hybrids and their in vivo analgesic and anti-inflammatory activity studies, *Bioorg. Med. Chem. Lett.*, 23 (5), 1306-1309, 2013.

[18] Dorostkar-Ahmadi, N., Bakavoli, M., Moeinpour, F. and Davoodnia, A. Investigation into the regiochemistry of some isoxazoles derived from 1,3-dipolar cycloaddition of 4-nitrobenzonitrile oxide with some dipolarophiles: A combined theoretical and experimental studies, *Spectrochim Act A Mol. Biomol. Spectrosc*., 79 (5), 1375-1380, 2011.

[19] Hu, Y. and Houk, K.N. Quantitative predictions of substituent and solvent effects on the regioselectivities of nitrile oxide cycloadditions to electron-deficient alkynes. *Tetrahedron*, 56 (42), 8239-8243, 2000.

[20] Himo, F., Lovell, T., Hilgraf, R., Rostovtsev, V. V., Noodleman, L., Sharpless, K. B. and Fokin, V. V., Copper (I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates, *J. Am. Chem. Soc.*, 127 (1), 210-216, 2005.

[21] Vieira, A. A., Bryk, F. R., Conte, G., Bortoluzzi, A. J. and Gallardo, H. 1, 3-Dipolar cycloaddition reaction applied to synthesis of new unsymmetric liquid crystal compounds-based isoxazole *Tetrahedron Lett.*, 50 (8), 905-908, 2009.

[22] Paudyal, M. P., Wu, L., Zhang, Z., Spilling, C.D. and Wong, C. F. A new class of salicylic acid derivatives for inhibiting YopH of Yersinia pestis, *Bioorg. Med. Chem*, 22 (24), 6781-6788, 2014.

[23] Datta, A., Walia, S. and Parmar, B. S., Some furfural derivatives as nitrification inhibitors, *Journal of Agricultural and Food Chemistry*, 49 (10), 4726-473, 2001.

[24] W. M. Haynes ed., "Physical Constants of Organic Compounds," in *CRC Handbook of Chemistry and Physics*, 97th Edition (Internet Version 2017), CRC Press/Taylor & Francis, Boca Raton, FL.

[25] Gaussian 09, Revision E.01, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Jr., Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö ., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

[26] Becke, A.D., Density−functional thermochemistry. The role of exact exchange, J. Chem. Phys., 98 (7) 5648-5652, 1993.

[27] Lee, C., Yang, W. and Parr, R.G, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density *Phys. Rev. B*, 37(2) 785-789, 1988.

[28] Vosko, S.H., Wilk, L. and Nusair, M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis, *Can. J. Phys*., 58 (8), 1200-1211, 1980.

[29] Stephens, P.J., Devlin, F.J., Chabalowski, C.F. and Frisch, M. J. Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields., *J. Phys. Chem.*, 98 (45), 11623-11627, 1994.

[30] Krishnan, R., Binkley, J. S., Seeger, R. and Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions, *J. Chem. Phys*., 72 (1), 650-654, 1980.

[31] Benchouk, W., Mekelleche, S. M., Silvi, B., Aurell, M.J. and Domingo, L.R., Understanding the kinetics solvent effects on the 1,3-dipolar cycloaddition of benzonitrile N-oxide: a DFT study, *J. Phys. Org. Chem.* 24(7), 611-618, 2011.