TOSMIC REAGENT: AN EXCELLENT PRECURSOR IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES

Damilola V. Aderohunmu^{1,2}, Taiwo T. Odutola¹, Olayinka O. Ajani^{1,2}
and Ezekiel F. Adebisi^{2,3,*}

¹ Department of Chemistry, CST, Covenant University, P.M.B. 1023, Ogun State, Nigeria.

² Covenant University Bioinformatics Research (CUBRe), Covenant University, Km 10 Idiroko Road, P.M.B. 1023 Ota, Ogun State, Nigeria

³ Department of Computer and Information Sciences, CST, Covenant University, P.M.B. 1023, Ogun State, Nigeria

* E-mail: ezekiel.adebiyi@covenantuniversity.edu.ng

ABSTRACT

Heterocycles are a major material in the world today, with a wide range of applications which include pharmaceutical, cosmetics, reprography, information storage, plastics, solvents, antioxidants, corrosion inhibition among others. The *p*-toluenesulfonylmethyl isocyanide (TosMIC) is a rich-rewarding synthetic agent making it valuable template in diverse synthetic applications. Synthetic utilization of TosMIC reagent as a precursor for accessing diverse heterocyclic compounds is worthy of note in the domain of applied research. This study is, therefore, tailored at a review of the progress of the TosMIC reagent as a starting material in the synthesis of heterocycles with well-endowed pharmacological activities.

Keywords: Heterocyclic Motifs, Isocyanides, Bioactive Molecule, Cyclization, Total Synthesis.

© RASAYAN. All rights reserved

INTRODUCTION

Isocyanide-initiated facile reactions are very useful in the synthesis of bioactive natural products which are a major requirement in drug development. One of such isocyanides is the TosMIC reagent which is a highly functionalized compound, containing one isocyano moiety, acidic hydrogen on the α -carbon atom and a sulphonyl group.¹ TosMIC reagent, also known as *p*-toluenesulfonyl methylisocyanide, is a crucial building block in synthetic chemistry and has been greatly engaged as an undeniable synthon for the preparation of a large array of 5-membered ring heterocycles² and in some cases, 6-membered types. The TosMIC reagent shows four different reactivities and is suited for forming many monocyclic heterocycles and benzo-fused heterocyclic compounds including thiophene, oxazole, triazole, indoles, imidazoles, pyrroles, among other.³ In addition, it also played a salient role in the preparation of ketonic molecules through alkylation followed by hydrolysis.⁴

Heterocyclic chemistry has gained tremendous attention because of its unavoidable pharmacological diversity in medicinal chemistry research.⁵ It is to meet this large amount of needs that newer and better yielding methods of synthesizing heterocyclic compounds are continuously being sought for by organic chemists. Heterocycles are of prime importance as a sub-discipline in organic chemistry. In the world today, millions of heterocyclic compounds are known with more being synthesized on continuous bases. For instance, there is a recent synthesis of per-O-acetyl and per-O-benzoyl glycosylthiocarbamide with reported antifungal activities.⁶ Hence, it is worthy to note that over 80% of commercially available drugs in the current market are made up of heterocyclic compounds which is a validation of their re-occurring nature in both the chemical and biological spheres as molecules of ubiquity. Thus, it is conceivable to highlight and review the valuable role of TosMIC in the synthesis of biologically active heterocyclic compounds which are the base of drug design.

Discovery of TOMIC Reagent

The word TosMIC which is going to be used for the sake of brevity, is an acronym obtained by systematic combination of the trivial name **Tosyl Methyl IsoCyanide** as shown in the bracket (Tos + M + I + C) which has IUPAC name 1-(isocyanomethyl sulfonyl)-4-methylbenzene⁷ is a reagent created by Dutch chemist, Prof. Leusen. It is of great application in organic synthesis due to its versatility in producing diverse pharmacophoric frameworks.⁸

Structure of TosMIC Reagent

The common technique which inserts reactive methylene group of TosMIC is the popular van Leusen three-component reaction (vL-3CR) producing 1,4,5-trisubstituted imidazoles.⁹ Owing to the structural diversity of TosMIC, it possesses dual-functional reactivity which means it can initiate reaction through reactive methylene initiated or the isocyano moiety enhanced resulting in diverse structural scaffolds.¹⁰ The main functional group in isocyanide has structural representation. The nitrogen and not the carbon atom is the point of linkage of CN which is as present in isomeric **nitrile**; hence, the prefix *iso*. The carbon atom of the isocyano group in TosMIC often exhibits carbene-like reactivity that is reflected in the resonance structure **1a** and its canonical hybrid **1b** (Fig.-1).¹¹

Fig.-1: Structure of TosMIC and Resonance Structures **1a** and **1b** of its Isocyanides

Preparation of TosMIC Reagent

TosMIC Reagent is prepared in a two-step reaction. The first step involved the reaction of sodium 4-methylbenzenesulfonate with formamide at 90-95 °C to produce *N*-(*p*-tolyl sulphonyl methyl) formamide, which consequently underwent dehydration in the presence of POCl₃ to form the required TosMIC (Scheme-1).¹²

Scheme-1: Synthetic Pathway towards TosMIC Reagent

Physical Properties of TosMIC Reagents

In terms of appearance, TosMIC reagent is a colorless, odorless solid⁸, which can be stored at room temperature without decomposition. TosMIC reagent is very stable, insoluble in water but relatively soluble in common organic solvents. It has a melting point of 109-113°C and molecular formula of C₉H₉NO₂S.¹³ It is however, soluble in some organic solvents.

Chemistry of TosMIC Reagents

TosMIC Reagent is applicable in the synthesis of heterocycles, it serves as a cyanation reagent, connecting agent and as Umpolung reagent for the synthesis of mono or disubstituted -CH₃ and -CH₂ respectively, as well as in three-component Ugi reaction.¹⁴ This is due to the functional groups it contains; a sulfinyl group that functions as a labile agent and enhances the acidic potential of the α-protons, an

isocyanide group, whose carbon atom is the core of many reactions and an active methylene group available for secondary reactions.¹ Some of the reported reaction techniques utilizing TosMIC, are Michael additions, cycloadditions and many cascade/tandem/multi- component reactions. Synthetic organic chemistry also involves selection and optimization of lead, synthesis and characterization of work for practical purposes.¹⁰

General Concept for Synthesis of Heterocycles

Heterocyclic compounds have always been a popular attraction in the field of medicinal chemistry research.¹⁵ Through the combinations of carbon, hydrogen and heteroatoms, heterocyclic compounds of diverse physical, chemical and biological properties are designed.¹⁶ The most common heterocyclic compounds are those having five- or six-membered rings and containing either, both or all of the heteroatoms - nitrogen, oxygen and sulphur.¹⁷ The general concept for the synthesis of heterocycles include the following: intramolecular substitution at saturated c-atom, intramolecular addition at carbonyl c-atom, intramolecular addition across other double bonds, cyclization at triple bonds, carbene and nitrene cyclization, electrocyclic reactions, ring closures involving ionic cyclization, important ring-closing reactions

Synthesis of Heterocycles via TosMIC Reagent

Although, various methods and techniques have been employed in the synthesis of bioactive heterocycles, the one of focus in this present work in the synthetic application of TosMIC Reagent. Despite the high versatility of TosMIC Reagent in heterocyclic synthesis, this Reagent has not been duly and resourcefully explored. Hence, it is noteworthy to expatiate on the synthesis of heterocyclic compounds by engaging TosMIC Reagent. It is also interesting to know that TosMIC has been successfully utilized in the synthesis of bioactive heterocycles such as oxazole, thiazole, pyrrole and derivatives, 1,2,4-triazole among others.

Synthesis of Pyrrole Derivatives

The Lamberth group reported that reaction of TosMIC with diethyl maleate in NaH and methyl iodide gave an intermediate dicarboxylated pyrrole which upon synthetic modification in some steps afforded the *N*-methyl-3,4-disubstituted pyrrole as shown in Scheme-2.¹⁸ It has been reported in another earlier study that sequential conjugate combination of TosMIC anion and 1-phenyl sulfonyl-1,3-butadiene was a valuable and direct route to the formation of 3,3'-bipyrrole. In a recent study, [3+2] cycloaddition with TosMICs and electron-deficient compounds provided a direct route to multi-substituted pyrrole derivatives.¹⁹

Scheme-2: Synthetic Pathway for *N*-Methyl-3,4-disubstitutedpyrrole

Synthesis of Thiazole Derivatives

One of the earliest synthetic procedures confirmed that the reaction of TosMIC with carbon disulfide will produce thiazoles.²⁰ In Scheme-3, TosMIC conveniently reacted with carbon disulfide in the presence of chloroform, tetrabutylammonium bromide (T-BAB) and NaOH. The intermediate thiazole product formed was successfully methylated with methyl iodide (MeI) to obtain the tosylated thiazole final product in excellent yield (90%) after washing and recrystallization of the relevant thiazole.²⁰

Scheme-3: Synthetic Pathway to 5-(Methylthio)-4-tosylthiazole

Synthesis of Imidazole Derivatives

Imidazole is a 5-membered heterocycle with nitrogen atoms situated in positions-1 and 3 of the ring. Earlier work of Van Leusen regarding the synthesis of 5-substituted-*N*-methylimidazole by three-component reaction with aldimines and TosMIC (Scheme-4) was duly captured in a recent review.²¹ A regioselective [3+2] annulation of CH₂ of isocyanides such as TosMIC with ketenimines was achieved in the base medium using *t*-BuOK or K₂CO₃ to derived 1,4,5-trisubstituted oxadiazole.²

Scheme-4: Synthetic Pathway to 5-Substituted-*N*-methylimidazole

Synthesis of Oxazole Derivatives

The treatment of cyano cyclohexane with benzoyl chloride at 60°C in neat condition was reported to produce an intermediate which was subsequently treated with *p*-toluenesulfonylmethyl isocyanide (TosMIC) reagent in NaH and tetrahydrofuran solvent at room temperature for 45 min to access biologically active 4-tosyloxazole derivatives.²² The route to the effective transformation of the intermediate through TosMIC to achieve biologically active product is as shown in Scheme-5.

Scheme-5: Synthetic Pathway to 5-Phenyl-4-tosyloxazole

Synthesis of Oxazoline Derivatives

Facile and un-hindered access to oxazoline derivative, 4-(4-tosyl-4,5-dihydrooxazol-5-yl)phenol, have been uncovered in a recent work wherein treatment of TosMIC with aromatic aldehydes were successfully achieved in the presence of imidazole catalyst (Scheme-6). It was worthy to note that the authors of this work were able to protect the oxazoline products from oxidation by using just water as a dual-purpose agent; having utilized it has both good solvent and antioxidant.²³

Scheme-6: Synthetic Pathway to 4-(4-Tosyl-4,5-dihydrooxazol-5-yl)phenol

Synthesis of (Z)-5-(1-Chloro-2-phenylvinyl)oxazole

Photochemical cyclization approach for the preparation of naphtho/heterobenz[2,1-d]oxazoles was achieved through the expected 4- and 2-phenyl substituted 5-arylethenyloxazoles which were synthesized from the required α,β -unsaturated aldehydes and tosylmethylisocyanide by the Van Leusen reaction as shown in Scheme-7.²⁴

Scheme-7: Synthetic Pathway to Naphtho[1,2-d]oxazole

Synthesis of Disubstituted-1,2,4-Triazoles

TosMIC reacted with diazonium salts under controlled conditions through base-induced cycloaddition at -10°C using K_2CO_3 in DMSO to yield a stereoisomeric mixture of 3-tosyl-1,2,4-triazole and 5-tosyl-1,2,4-triazole derivatives in 80% and 12% yields respectively.³ The reaction conditions and structural representation of the mixtures of the two products are as shown in Scheme-8.³

Scheme-8: Synthetic Pathway to Mixture of Tosylated-1,2,4-Triazole

Synthesis of Pyrrolo[1,2-c]pyrimidines

It is also possible to utilize TosMIC for the conversion of one small heterocycle to another bigger one. For instance, the reaction of TosMIC with pyrrole-2-carboxaldehyde in the presence of DBU base using tetrahydrofuran (THF) solvent afforded pyrrolo[1,2-c]pyrimidine.²⁵ The reaction product was achieved in 82% through stirring of the mixture at ambient condition for 2 h and then neutralized with acetic acid (Scheme-9). It was recrystallized from CH_3CN to give the desired product.²⁵

Scheme-9: Synthetic Pathway to Pyrrolo[1,2-c]pyrimidines

Synthesis of Indole Derivatives

Michael acceptors and alkenyl substituted TosMIC homologs reacted to produce 2,3-dialkenyl substituted pyrroles. The trisubstituted pyrrole intermediate was made to undergo ring closure in the basified medium under UV light influence and subsequent dehydrogenation to produce tetrasubstituted indole as shown in Scheme-10.³

Scheme-10: Synthetic Pathway to 1,3,5,7-Tetrasubstituted Indole

Synthesis of 2-Acetylchromeno[3,4-c]pyrrol-4(2H)-one

3-Acetylcoumarin was prepared by Knoevenagel combination of ethyl acetoacetate with salicylaldehyde under the influence of piperidine catalyst as we earlier reported.⁵ Further treatment of 3-acetylcoumarin with TosMIC had been reported to afford 2-acetyl chromeno[3,4-c]pyrrol-4(2H)-one in the presence of triethylamine (Et₃N) and piperidine after stirring at room temperature for 8 h in DMF solvent (Scheme-11).²⁶

Scheme-11: Synthetic Pathway to 2-Acetylchromeno[3,4-c]pyrrol-4(2H)-one

Synthesis of Isoquinoline Natural Product (Papaverine)

TosMIC Reagent is very useful in the total synthesis of phytochemicals which are secondary metabolites such as papaverine, mansouramycin B, muscalure among others. Papaverine which is an approved drug template in the treatment of gastrointestinal tract and in muscle relaxation was synthesized by a reaction of veratraldehyde with TosMIC. The isonitrile derivative formed is reacted with veratraldehyde acetal in CF₃COOH, towards accessing an amide derivative which is subsequently transformed to papaverine which is an isoquinoline derivative (Scheme-12).²⁷

Scheme-12: Synthetic Pathway to Papaverine

Selected Bioactive Heterocycles accessible via TosMIC

Indole-3-ethanamide chromophore **1** which was accessed through the condensative reaction of Tosylmethylisocyanide with 3-formylindole was an antifungal drug.²⁸ TosMIC provided the essential support in the synthesis of **2** which was reported to possess antidiabetic activity by targeting the target glucose-6-phosphate translocase.⁹ Vertex's hepatitis C drug candidate VX-497, merimepodib **3** was prepared by the condensation of the aldehyde with TosMIC to afford the expected oxazole **3**.²⁹ The imidazole derivative **4** was reported to be potent anticancer agent with IC₅₀ of 0.46 M.²¹ Total synthesis of Mansouramycin B, which was a potent antibiotic and antitumor agent, was achieved through TosMIC route.³⁰ In similar manner papaverine which was designed and prepared through TosMIC route is a muscle relaxant drug (Fig.-2).

CONCLUSION

TosMIC is specially, interesting because of its magical potential in the synthesis of bioactive heterocycles and other organic scaffolds used in drug design. Heterocyclic compounds are the structural framework in therapeutic medicine for drug design and development. Based on their widespread application in medicinal chemistry research, an array of literature has been accumulated. It is, therefore, very crucial to create more awareness in the potential utilization of TosMIC reagent in development of new series of

biologically active heterocycles to help the man in his continuous combat against microbial infections and various terminal diseases.

Fig.-2: Some Heterocyclic Compounds with Notable Biological Activities

ACKNOWLEDGMENT

This work was supported by the National Institutes of Health (Grant No: 1U2RTW010679). Covenant University is gratefully acknowledged for the support for this work.

REFERENCES

1. P. R. Krishna, E. R. Sekhar, and Y. L. Prapurna, *Tetrahedron Letters*, **48**, 9048(2007), DOI:10.1016/j.tetlet.2007.09.164.
2. J. Cai, H. Bai, Y. Wang., X. Xu, H. Xie, and J. Liu, *Chemical Communication*, **55**, 3821(2019), DOI:10.1039/c9cc01257e.
3. Synthatex Fine Chemicals Ltd., 2018. Tos MIC and derivatives in organic synthesis, Accessed October 12, 2018. Available online at www.synthatex.com
4. A. Dömling, Toluene sulphonylmethyl isocyanide (TOSMIC) and the Van Leusen MCR. *Organic Chemistry Highlights*, 2005, Available online at <http://www.organic-chemistry.org/Highlights/2005/05May.shtm>
5. O.O. Ajani, O. Ajayi, J.A. Adekoya, T.F. Owoeye, B.M. Durodola, and O.M. Ogunleye, *Journal of Applied Sciences*, **16**(3), 77 (2016), DOI:10.3923/jas.2016.77.87.
6. S.S. Kadu and G.V. Korpe, *Rasayan Journal of Chemistry* **12**(3), 1058 (2019), DOI:10.31788/RJC.2019.1235128.
7. NextBio, 2018. Accessed October 16, 2018, Available online at www.nextbio.org
8. D. van Leusen, and A.M. van Leusen, *Organic Reactions*, **57**, 419 (2001), DOI:10.1002/0471264180.or057.03.
9. S. Bräuer, M. Almstetter, W. Antuch, D. Behnke, R. Taube, P. Furer, and S. Hess, *Journal of Combinatorial Chemistry*, **7**, 218 (2005), DOI: 10.1021/cc049867+
10. B. Geetha, G. Swarnalatha and G.V. Subba Reddy, *Rasayan Journal of Chemistry*, **12**(3), 1063 (2019), DOI:10.31788/RJC.2019.1235165a.

11. A. Lygin, Ph.D Thesis, Department of Chemistry, Georg-August-Universität, Göttingen, Germany (2009).
12. B. Hoogenboom, O. Oldenziel, and A.M. Leusen, *Organic Syntheses Collection*, **6**, 987 (1988), DOI:10.15227/orgsyn.057.0102.
13. ChemExper Chemical Directory, 2018, Accessed October 10, 2018, Available online at <http://www.chemexper.com/chemicals/supplier/cas/36635-61-7.html>
14. C.G. Neochoritis, D. Livadiotou, V. Tsiaras, T. Zarganes-Tzitzikas, and E. Samatidou, *Tetrahedron*, **72(33)**, 5149 (2016), DOI:10.1016/j.tet.2016.07.013.
15. O.O. Ajani, F.E. Owolabi, G.E. Jolayemi, I.O. Olanrewaju, and D.V. Aderohunmu, *Rasayan J. Chem.*, **10(4)**, 1402 (2017), DOI:10.7324/RJC.2017.1041816.
16. E. Vitaku, D.T. Smith, and J.T. Njardarson, *Journal of Medicinal Chemistry*, **57(24)**, 10257 (2014), DOI:10.1021/jm501100b.
17. K. Fauché, L. Nauton, L. Jouffret, F. Cisnetti, and A. Gautier, *Chemical Communications* **53**, 2402(2017), DOI:10.1039/c6cc09160a.
18. H. Walter, C. Lamberth, and C. Corsi, *Monatshefte Chemie*, **149(4)**, 791 (2018), DOI:10.1007/s00706-017-2101-y.
19. Z. Ma, Z. Ma, and D. Zhang, *Molecules*, **23(10)**, 2666 (2018), DOI:10.3390/molecules23102666.
20. A. Leusen, J. Wilderman, and H. Oldenzeil, *Journal of Organic Chemistry*, **42(7)**, 1153(1977), DOI:10.1021/jo00427a012.
21. I. Ali, M.N. Lone, and H.Y. Aboul-Enein, *Medicinal Chemistry Communications*, **8(9)**, 1742 (2017), DOI:10.1039/c7md00067g.
22. M. Talebizadeh, A. Darehkordi, and M. Anary-Abbasinejad, *Arkivoc*, **v**, 194 (2018), DOI:10.24820/ark.5550190.p010.556.
23. R. Abraham, P. Prakash, K. Mahendran, and M. Ramanathan, *Arabian Journal of Chemistry*, (2018), DOI:10.1016/j.arabjc.2018.03.022
24. I. Šagud, M. Šindler-Kulyk, I. Škorić, V. Kelava, and Ž. Marinić, *European Journal of Organic Chemistry*, 3326 (2018), DOI:10.1002/ejoc.201800737.
25. J.M. Minguez, J.J. Vaquero, J.L. Garcia-Navio, and J. Alvarez-Builla, *Tetrahedron Letters*, **37(24)**, 4263 (1996), DOI:10.1016/0040-4039(96)00812-x.
26. A. Shaabani, H. Sepahvand, A. Bazgir, and H.R. Khavasi, *Tetrahedron* **74**, 7058 (2018), DOI:10.1016/j.tet.2018.10.039.
27. C.D. Gilmore, K.M. Allan, and B.M. Stoltz, *Journal of the American Chemical Society*, **130**, 1558 (2008), DOI:10.1021/ja0780582.
28. B. Beck, S. Hess, and A. Dömling, *Bioorganic and Medicinal Chemistry Letters*, **10(15)**, 1701 (2000), DOI:10.1016/s0960-894x(00)00305-x
29. R.J. Herr, D.J. Fairfax, H. Meckler, and J.D. Wilson, *Organic Process Research and Development*, **6(5)**, 677 (2002), DOI:10.1021/op025546f.
30. A. Coppola, D. Sucunza, C. Burgos, and J.J. Vaquero, *Organic Letters*, **17(1)**, 78 (2015) DOI:10.1021/ol5032624.

[RJC-5315/2019]