Benefits of Using TosMIC in Various Applications

Abstract

With three important chemical groups—specifically, an isocyanide, a tosyl and an acidic α-carbon in-between—contained within its structure, TosMIC (CAS# 36635-61-7) is a versatile synthetic reagent and building block in organic synthesis. This technical whitepaper highlights three mission-critical industrial applications, namely TosMIC's roles in converting carbonyl groups to nitriles as a cyanating reagent; synthesizing heterocyclic compounds such as oxazoles, imidazoles and pyrroles; and preparing Knoevenagel-type condensation products.

Background

Tosylmethyl isocyanide[i], or TosMIC, is a colorless solid that can be stored at room temperature without decomposing. Unlike other isocyanides however, TosMIC is effectively odorless[1]. It has a melting point of 111–113 °C, and is insoluble in water but soluble in organic solvents such as dimethoxyethane (DME) and tetrahydrofuran (THF)[2,3].

Structurally, as may be seen in Figure 1, TosMIC's versatility stems from three key components: the isocyanide (blue) and tosyl (pink) groups, and the acidic *α*-carbon (red). The isocyanide, which undergoes addition-type reactions, has a carbon atom that usually acts as an electrophilic center for ring-closing reactions (and may double as an active methylene group for secondary reactions)[1,4,5]. This carbon atom also typically exhibits carbene-like reactivity, which is reflected in the first resonance structure and its canonical hybrid on the right[6]. Regarding the tosyl, it acts as a good leaving group in the generation of heterocycles[4]. Finally, the *α*-position's reactivity stems from the strong electron-withdrawing effects of the other two groups (though the *α*-position is also less sterically hindered)[1,7]. With $pK_a \approx 14$, the acidic *α*-carbon is readily deprotonated under basic conditions to yield the carbanion $TosC^-HNC$—on which this whitepaper's TosMIC-based applications base their initial reactions[8,4]. Related anions may be derived from mono-substituted $TosCHR^1NC$ (formed via S_N2 substitution reactions involving $TosC^-HNC$ and an alkyl halide electrophile) and used to prepare di-substituted $TosCR^1R^2NC$ TosMIC derivatives[4,7]. In this way, TosMIC can synthesize ketones via di-substitution at the *α*-position followed by hydrolysis, or act as a connecting reagent of two alkyl halides via di-substitution followed by reduction (e.g., using Li and NH_3)[4]. Otherwise, in the presence of a dipolarophile (e.g., alkene, carbonyl, imine), the 1,3-dipolar character of TosMIC is exploited in a [3+2] cycloaddition reaction[7,4]. However, $TosCHR^1NC$ cannot be used in the reductive cyanation or Knoevenagel procedures because those require both *α*-carbon hydrogens[4].

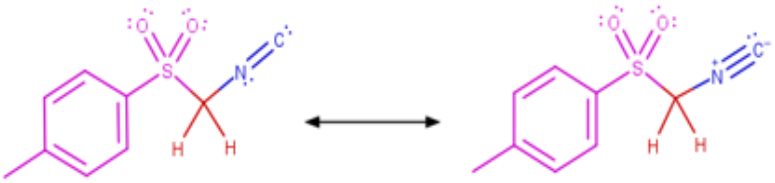

Figure 1. Resonance Structures of TosMIC.

TosMIC is an exceptionally useful material in a variety of applications, and three usage groups are described briefly below.

Representative Cases of TosMIC as a Value-added Differentiator

[i] Other names include *p*-toluenesulfonylmethyl isocyanide, *p*-tolylsulfonylmethyl isocyanide, 4-tolylsulfonylmethyl isocyanide, and the IUPAC-designated 1-(isocyanomethylsulfonyl)-4-methylbenzene.

Usage 1: Reductive Cyanation

Reductive cyanation of ketones to cyanides occurs upon reaction with TosMIC and base (e.g., *t*-BuOK) in aprotic solvents (e.g., DME, THF)[4]. This process is sped up considerably in the presence of 1–2 eq. MeOH or EtOH, while an excess of base is used to suppress possible cyclodimerization reactions involving TosMIC[9,10,11,12]. Reaction temperatures range from 0–50 °C, depending on the ketone's reactivity[10]. Structurally, the cyano group's carbon atom is TosMIC's α-carbon[10]. TosMIC-based reductive cyanation of ketones has seen considerable use in generating precursors to pharmaceutical compounds.

Reductive cyanation also works on aldehydes but changing the ketonic reaction conditions is necessary to avoid low yields[4]. The aldehyde should still be reacted with TosMIC under basic and aprotic conditions, but at low temperatures (-50 to -20 °C)[4]. Upon addition of excess methanol, the reaction can then be completed by heating (e.g., under reflux)[13,14]. Beside the Pharmaceutical industry, TosMIC-based reductive cyanation processes have found use in the Flavors & Fragrances industry for preparing active perfuming ingredients—among other industries. The reaction mechanism for reductive cyanation of ketones and aldehydes may be found in the literature[9,10,15].

Usage 2: Direct Synthesis of Heterocycles

The TosMIC-based van Leusen synthesis methods for oxazole-, imidazole- and pyrrole-based compounds, all of which involve a base-mediated [3+2] (also labeled "1,3-dipolar") cycloaddition reaction, are some of the most convenient and attractive due to simple operation, easily obtained raw materials and a broad substrate scope[16,17,18]. The van Leusen method for oxazoles involves reacting TosMIC (or TosCHR[1]NC), in alcoholic solvents, with aldehydes and base[4]. One procedure generally used to synthesize oxazoles involves reacting the aldehyde, TosMIC and the base K_2CO_3 in methanol solvent and heating to reflux[19,4]. This process was noted as being suitable for the manufacturing of oxazole precursors to spleen tyrosine kinase (Syk) inhibitors[20]. An approximate reaction scheme is shown in Figure 2, in which the final step is a base-promoted elimination[21].

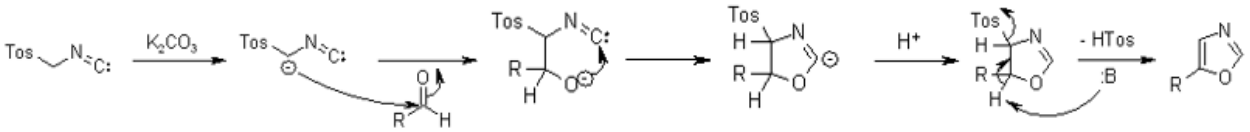

Figure 2. Reaction Mechanism of the van Leusen Oxazole Synthesis.

Closely related to the above method for oxazole generation is the van Leusen method for synthesizing imidazoles from imines and TosMIC. The reaction of TosCHR[1]NC with aldimines, usually prepared from aromatic aldehydes and aliphatic amines in the context of van Leusen synthesis, yields the otherwise-elusive 1,4,5-trisubstituted imidazoles[11,22]. A method suitable for industrial processes, in which TosMIC does not have to be isolated (and is a safer method for obtaining 5-substituted oxazole and imidazole compounds), involves reacting TosMIC with the aldehyde or imine (e.g., aldimine), along with base, in a mixed aprotic-protic solvent[19]. Oxazole- and imidazole-based compounds are useful in agrochemicals and pharmaceuticals.

To prepare pyrroles, TosMIC (or TosCHR[1]NC) undergoes cycloadditions with Michael acceptors (prepared from aldehydes and activated methyl or methylene groups)[4]. It is sometimes advantageous to increase the Michael acceptor reactivity by using two electron-withdrawing groups (instead of just one); to form a pyrrole, the stronger leaving group of the two (located at the same carbon atom) is removed during the reaction[4]. This "leaving group procedure" has been followed in the preparation of certain industrially-relevant agrochemicals. Pyrroles have otherwise found use in pigments and materials science applications, and heterocycles, in general, have many applications in various industries such as pharmaceuticals, cosmetics, reprography, information storage, plastics, solvents, antioxidants and corrosion inhibition[23,3].

Usage 3: Preparation of Knoevenagel-type Condensation Products

Reaction of ketones or aldehydes with TosMIC and base (e.g., *t*-BuOK), at low temperatures (-70 to -40 °C) in aprotic solvents (e.g., THF), leads to 1-tosyl-substituted *α*,*β*-unsaturated formamides[24,25,26,27]. Subsequent dehydration (e.g., using $POCl_3$ and *i*-Pr_2NH) gives 1-tosyl-substituted *α*,*β*-unsaturated isocyanides, sometimes called Knoevenagel-type condensation products, which are extensively used as TosMIC homologs and as Michael acceptors for pyrrole synthesis[4]. The precursor and product are shown in Figure 3.

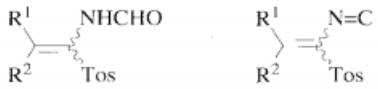

Figure 3. Structures of a 1-tosyl-substituted *α*,*β*-unsaturated formamide (left) and Knoevenagel-type condensation product (right).

A representative use case for this application is an improved production method, in which the intermediate *α*,*β*-unsaturated formamide compound is prepared from a ketonic precursor, for manufacturing the steroid progesterone[28]. In another recently published method for manufacturing progesterone, the intermediate Knoevenagel product compound is prepared directly from the ketonic 4-androstenedione (4AD was seemingly less expensive than the traditionally-used starting material)[29]. One industrial application of converting an aldehyde to a Knoevenagel product is found in some syntheses of the pharmaceutical compound papaverine[30].

For preparation of the same imidazole, reacting TosMIC with an aldehyde to get a Knoevenagel product before reacting that with an amine has given higher yields than for the corresponding direct synthesis (mentioned previously) via TosMIC[25].

Varsal Advantage

Varsal is one of the world's leading producers of TosMIC, and has best-in-class capabilities for consistent, large-scale, pharma-grade TosMIC production. We are differentiated from the competition as Varsal's proprietary manufacturing logistics processes allows us to produce consistent, stable, extremely-high-purity material with low residual impurities, low loss on drying, and low residue on ignition—leading to maximal yield and product quality for Varsal's customers.

Low residual impurities in TosMIC are important to optimize the final product's consistency, yield, and quality. Every situation is different, but a use case for why low residual impurities in TosMIC are important is that *p*-toluenesulfinic acid (TosH), with $pK_a \approx 1.66$, is a much stronger acid than TosMIC[31]. As such, TosH would more readily deprotonate in base, depleting the amount of base available for deprotonating TosMIC. The result would be lower yields for TosC⁻HNC, which, as mentioned previously, is the product of the first reaction step for all three whitepaper usage groups.

A low loss on drying (LOD) is important technically because the LOD represents a chemical sample's total moisture content[32]. TosMIC is moisture-sensitive and therefore more subject to degradation in the presence of greater moisture. Controlling the moisture content is also important in the quality preparation of, e.g., pharmaceuticals, foodstuffs and plastics[33]. In the case of active pharmaceutical ingredients (APIs), the moisture content affects the physical and chemical properties of pharmaceutical finished dosage forms, and is therefore important to control by limiting the amounts introduced by reagents and/or precursors like TosMIC.

Finally, a low residue on ignition would indicate a low amount of inorganic impurities, which in TosMIC's case includes heavy metals[34]. These metal impurities can potentially contaminate medicine or

supplement products, and it would therefore be important to control and limit the amounts introduced to manufacturing processes by chemicals like TosMIC[35].

In conclusion, Varsal is able to serve a wide variety of end-markets and applications, as our intimate knowledge of the manufacturing process allows us to custom-manufacture various grades of TosMIC tailored to our customers' requirements. Please contact us at info@varsal.com to learn more about how Varsal can help you solve your complex chemical and specialty intermediates challenges!

[1] Org. Biomol. Chem., 2019, **17**, 6735
[2] http://www.chemexper.com/search/cas/36635617.html
[3] "TosMIC Reagent: An Excellent Precursor in the Synthesis of Biologically Active Heterocycles"
[4] "Synthetic Uses of Tosylmethyl Isocyanide (TosMIC)." Daan van Leusen and Albert M. van Leusen.
[5] P. R. Krishna, E. R. Sekhar, and Y. L. Prapurna, *Tetrahedron Letters*, **48**, 9048 (2007).
[6] A. Lygin, Ph.D Thesis, Department of Chemistry, Georg-August-Universität, Göttingen, Germany (2009).
[7] "Unexpected Role of p-Toluenesulfonylmethyl Isocyanide (TosMIC) as a Sulfonylating Agent in Reactions with alpha-Bromo Carbonyl Compounds."
[8] "p-Toluenesulfonylmethyl Isocyanide (TosMIC)". V. V. Ramana Reddy.
[9] https://www.organic-chemistry.org/namedreactions/van-leusen-reaction.shtm
[10] Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
[11] van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem*. **1977**, *42*, 1153.
[12] Bull, J. R.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2151.
[13] van Leusen, A. M.; Oomkes, P. G. *Synth. Commun.* **1980**, *10*, 399.
[14] Garrigues, B.; Oussaid, B.; Hubert, C. *Bull. Soc. Chim. Fr.* **1993**, *130*, 58.
[15] van Leusen, D.; van Leusen, A. M. *Recl. Trav. Chim. Pays Bas* **1991**, *110*, 402.
[16] "Recent Advances in the Synthesis of Oxazole-Based Molecules via van Leusen Oxazole Synthesis."
[17] "Synthesis of Imidazole-Based Medicinal Molecules Utilizing the van Leusen Imidazole Synthesis."
[18] "Synthesis of Multi-Substituted Pyrrole Derivatives Through [3+2] Cycloaddition with Tosylmethyl Isocyanides (TosMICs) and Electron-Deficient Compounds."
[19] "Process for producing 5-substituted oxazole compound and 5-substituted imidazole compound." Hidekazu Miyazaki, Nobuo Matsui, Atsushi Ogiwara, Hiroshi Sakai.
[20] "Oxazole derivatives that inhibit Syk." Alain Moussy, et al.
[21] https://www.organic-chemistry.org/namedreactions/van-leusen-oxazole-synthesis.shtm
[22] Possel, O.; van Leusen, A. M. *Heterocycles* **1977**, *7*, 77.
[23] "Synthesis of pyrroles." Brian L. Pagenkopf and Ming Yu.
[24] Schöllkopf, U.; Schröder, R.; Blume, E. *Justus Liebigs Ann. Chem.*, **1972**, *766*, 130.
[25] Leusink, F. R., Ph.D. Thesis, Groningen University, 1993.
[26] Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 311.
[27] van Leusen, A. M.; Schaart, F. J.; van Leusen, D. *Recl. Trav. Chim. Pays Bas* **1979**, *98*, 258.
[28] "A kind of preparation method of progesterone." Liang Xiao Min, et al.
[29] "A kind of method for preparing progesterone." Wang You Fu, et al.
[30] Barrett, A. G. M.; Barton, D. H. R.; Falck, J. R.; Papaioannou, D.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. I* **1979**, 652.
[31] "p-Toluenesulfinic Acid." Gregory S. Hamilton.
[32] "Loss-on-Drying Method (LOD)." Dr. Liji Thomas, MD.
[33] "Drying Oven vs. HMA Whitepaper." Mettler-Toledo AG.
[34] "29(2) Interim Revision Announcement: <281> RESIDUE ON IGNITION."
[35] "Metal impurities in food and drugs." Abernethy, et al.