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p-Tolylsulfonylmethyl Isocyanide (TosMIC) – a Versatile Formaldehyde Equivalent with Reversed Polarity

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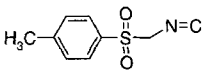
p-Tolylsulfonylmethyl isocyanide (TosMIC) (**1**), a stable, crystalline and odourless isonitrile, combines a number of unique chemical properties and has therefore been developed into a synthon of diverse utility [1].



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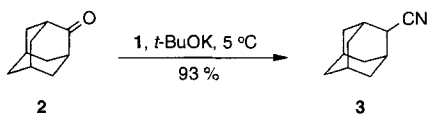
Basically, TosMIC is a masked formaldehyde derivative in form of a N,S-acetal. The electronegative influence of the tosyl and isocyano groups facilitates the formation of the TosMIC anion and therefore effects an umpolung of carbonyl reactivity. TosMIC can be used as a formyl-(di)anion equivalent, whereas mono-substituted TosMIC derivatives are versatile acyl-anion equivalents.



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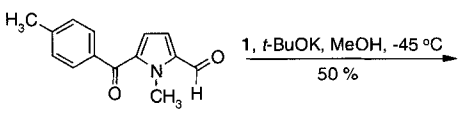


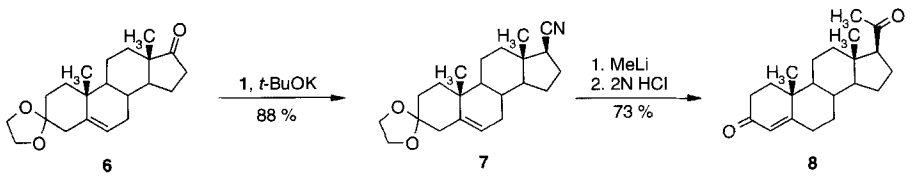
4 **5**

Ketones are generally converted with TosMIC and potassium *t*-butoxide in one step into nitriles, as exemplified for the preparation of 2-cyanoadamantane (**3**) [2]. Only sterically hindered or readily enolizable ketones do not undergo this reaction called reductive cyanation. The corresponding transformation of aldehydes needs addition of methanol in the final stage of the process. The conversion of **4** → **5** rationalizes the higher reactivity of aldehydes compared to ketones regarding TosMIC, also demonstrated by the much lower reaction temperature [3].

The one or two carbon homologation of the 17-oxo steroid **6** by reductive cyanation allows a very short approach to the pregnancy hormone progesterone (**8**) [4].

The Knoevenagel-type condensation of ketones with TosMIC represents another appropriate possibility for the introduction of a carbon side chain into steroids, as demonstrated by the synthesis of **11** [5]. In contrast to the reductive cyanation, the Knoevenagel condensation product is formed by elimination of one eqivalent of water [6]. Therefore, this reaction needs the additional support of a dehydrating agent.

One of the most important features of TosMIC is, that it enables the easy synthesis of several aromatic and non-aromatic heterocyclic systems, mainly azoles. Of special interest is the preparation of pyrroles, which has found ample



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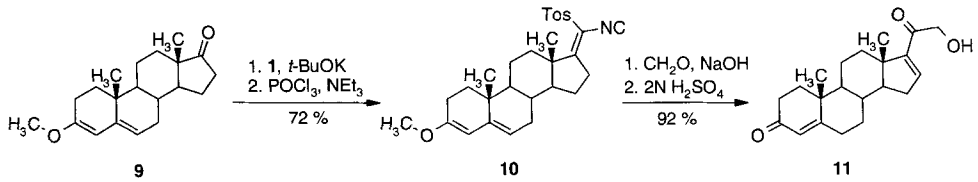
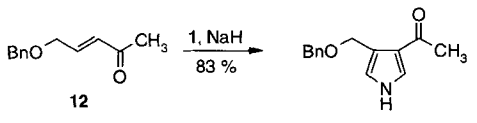


9 **10** **11**

application. The key steps of the syntheses of verrucarin E, an antibiotic produced by the soil fungus *Myrothecium verrucaria* (**12** → **13**) [7] and porphobilinogen, the biosynthetic precursor of all naturally occuring porphyrins and corrins like hemoglobin and chlorophyll (**14** → **15**) [8], rely on the base-induced cycloaddition of TosMIC to Michael acceptors. This so-called van Leusen pyrrole synthesis is not limited to the use of the usual α,β-unsaturated carbonyl or carboxyl compounds as Michael acceptors. Also the Knoevenagel condensation products of TosMIC and aldehydes are applicable to Michael reactions with *C*-nucleophiles. The 2,3-dichlorostyrene derivative **16** undergoes a reaction with ethyl cyanoacetate to provide the widely employed seed-protecting fungicide fenpiclonil **17** in a very short way [9].



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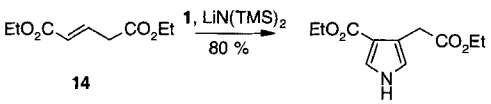

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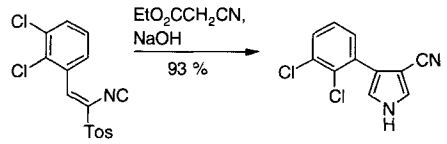


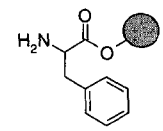
16 **17**

The basic principle of the van Leusen pyrrole synthesis is, that α-metallated TosMIC possesses a nucleophilic center, which may add to polar multiple bonds, and an electrophilic center, the isocyanide group, which allows subsequent heterocyclization. This transfer of the CH–N=CH unit of TosMIC is not restricted to electron deficient alkenes. Imidazoles are obtained analogously from imines [10], oxazoles from aldehydes [11] or carboxylic acid chlorides and anhydrides [12], thiazoles from dithioesters [13] or carbon disulfide [14], 1,2,4-triazoles from diazonium salts [15] and pyridines from cyclopropenylium salts [16].

In peptide synthesis, TosMIC was used as isocyanide component in the Ugi four component condensation reaction [17]. This one pot conversion combines an aldehyde, an amine, a carboxylic acid and an isonitrile to form an α-acylamino amide with generation of a new stereocenter derived from the aldehyde moiety. The following example demonstrates the application of TosMIC in the stereoselective solid phase synthesis of pharmacologically important 2,5-diketopiperazines like **22** [17a].

Another asymmetric TosMIC reaction was reported with the tolualdehyde-chromium-tricarbonyl complex **23** [18]. This chiral complex reacts with TosMIC to form exclusively one **24** of the four possible oxazolines, indicating complete

18 **19**



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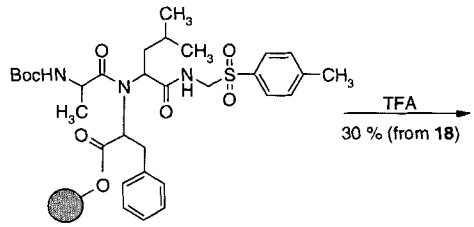

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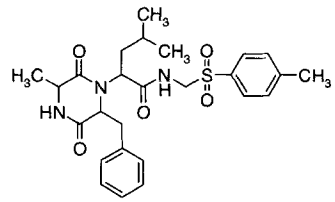

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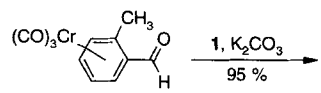
diastereoselectivity through asymmetric induction. Decomplexation followed by reduction provides the (+)-*S*-halostachine analogue **25** in optically pure form.



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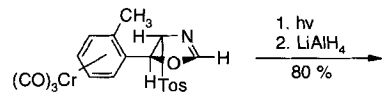

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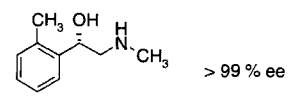

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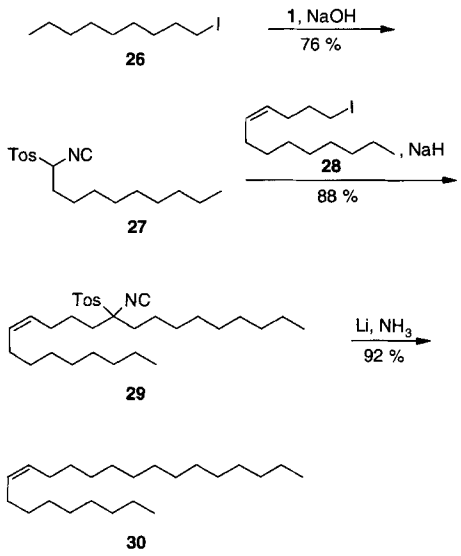
The two methylene hydrogens of TosMIC can be replaced consecutively by base-induced alkylation [19], representing an umpolung of carbonyl reactivity. This fact has been exploited for instance in the short syntheses of muscalure **30**, a pheromone of the common house fly and (–)*exo*-brevicomin, a pheromone of the Western pine beetle [20]. In the route to

muscalure, the two alkyl halides **26** and **28** are connected by the TosMIC methylene group. Subsequent reduction of the tosyl- and isocyano-substituted hydrocarbon **29** with lithium in liquid ammonia provides the target compound **30**.



This principle of using TosMIC as a connective reagent is also used for the synthesis of otherwise not easily obtainable cycloalkanones [21] and symmetrical and unsymmetrical acyclic diketones [22].

TosMIC is for some time commercially available, but it can also be easily prepared by Mannich reaction from sodium *p*-toluenesulfinate and formamide [23]. Alternatively, α-lithiomethyl isocyanide can be sulfonylated with tosyl fluoride to obtain TosMIC [24]. Besides several other derivatives, also ^{13}C- [7], ^{14}C- [2b] and ^{15}N-labeled [25] TosMIC compounds have been reported.

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