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An Efficient Method For The Synthesis Of Substituted TosMIC Precursors

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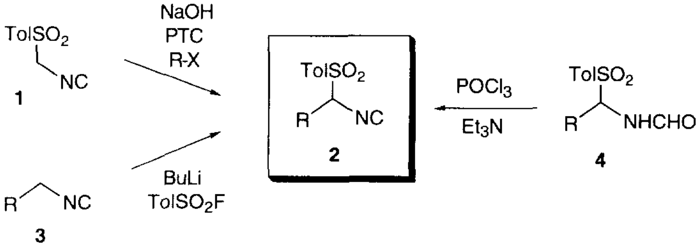
Abstract: Substituted tosylmethyl isocyanides (TosMICs) are useful reagents for which no general method of preparation is available. We describe here a high-yielding method for the synthesis of substituted tosylmethyl formamides, which are readily converted to the corresponding isocyanides. Copyright © 1996 Elsevier Science Ltd

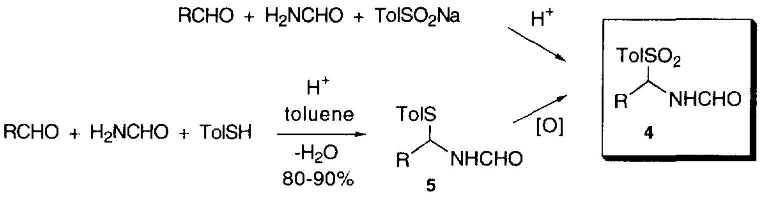
The wide array of structures available using TosMIC (**1**) make it an extremely valuable and versatile reagent.[1] Isonitriles such as **2**, however, wherein $R \neq H$ have been used far less frequently, largely owing to the lack of a general method for their synthesis. van Leusen[2] has shown that TosMIC (**1**) can be alkylated under phase transfer conditions to provide **2** (R = alkyl) (Scheme 1), although this adds a step and only works well with primary halides . In addition, this method is unsuitable for isocyanides **2** wherein R = Ar or *t*-Bu. An alternative method[3] involves deprotonation of isocyanide **3** with BuLi and reacting with TosF. The stench and toxicity of alkyl isocyanides, as well as the cost of TosF, are significant drawbacks of this method. The most straightforward method[4] involves dehydration of tosyl formamides **4**, most commonly by using $POCl_3$.[5] Developing a simple, high-yielding protocol to prepare tosyl formamides **4** is the topic of this Letter.

SCHEME 1



We recently required a method for preparing multi-kilogram quantities of reagent **2** (R = 4-F-Ph). Despite the low yield typically reported for preparing formamides **4** (R≠H), we felt that this method is the most direct and potentially least expensive. A review of the literature revealed that formamides **4** are most commonly prepared by one of two methods (Scheme 2). Heating benzaldehyde, formamide and sodium *p*-toluenesulfinate in aqueous acid is reported to provide **4** (R = Ph) in 84% yield.[4,6] However, in our hands, yields greater than 50% were never obtained. More importantly, the reaction failed completely with 4-fluorobenzaldehyde. A second strategy involves heating *p*-thiocresol, formamide and the aldehyde in toluene with acid catalysis and azeotropic removal of water to generate the sulfide **5** in high yields.[7] These sulfides have been oxidized (when R = H) to sulfones **4** using *m*-CPBA or H_2O_2.[8] However, this method has only been reported for **4** (R = H) and failed completely for us when R = 4-F-Ph.

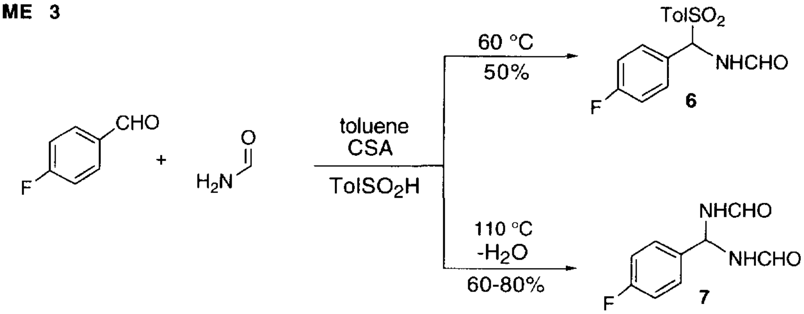
SCHEME 2



We report here an optimized, one-pot synthesis of formamides **4** which are precursors to the substituted TosMIC derivatives. Most importantly, this method works best for those compounds which are difficult to prepare by the methods mentioned above.

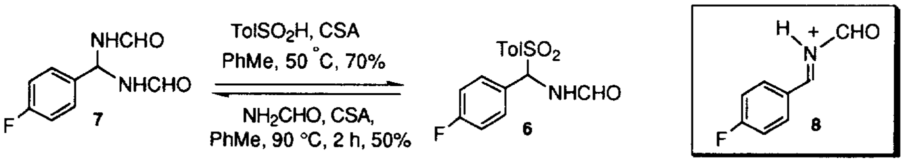
Our initial efforts focused on preparing **6** by employing the conditions used in the synthesis of sulfide **5** (Scheme 3). Heating 4-fluorobenzaldehyde, formamide, a catalytic amount of camphorsulfonic acid and freshly prepared *p*-toluenesulfinic acid (from the Na^+ salt) with no solvent or minimal amounts of toluene at 60 °C generated **6** in yields which never exceeded 50%. However, conducting the same reaction at 110 °C with azeotropic removal of water provided none of the expected product, but formed the bis-formamide **7** instead.

SCHEME 3



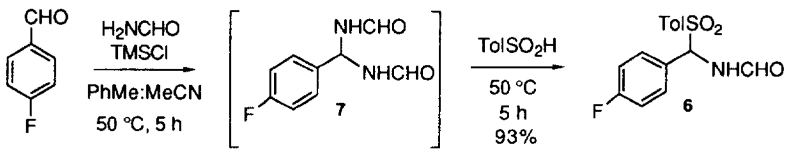
We have rationalized these results by assuming that an equilibrium between **6** and **7** is established under the reaction conditions, with the putative *N*-formyliminium ion **8** as the central intermediate.[9] Indeed, heating the bis-formamide **7** with *p*-toluenesulfinic acid at 50 °C in toluene produced the tosylformamide **6** in 70% yield (Scheme 4). Conversely, at higher temperatures the adduct **6** is transformed to the bis-formamide **7** in the presence of 2 equivalents of formamide. From these results it became clear that if temperature was closely monitored, bis-formamides **7** could be useful precursors to tosylformamides **6**. Moreover, we believed that conditions to convert aldehydes to tosylformamides **4**, via bis-formamides **7** formed *in situ*, could be developed.

SCHEME 4



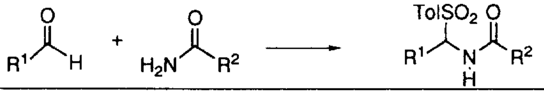
Of the reported syntheses of bis-amides similar to **7**[10], we were most interested in a report from Zavyalov[11] in which aldehydes were converted to bis-amides by stirring in DMF with TMSCl and primary amides at 25 °C. While this method provided the bis-formamide **7** in high yields, direct addition of *p*-toluenesulfinic acid to the reaction failed to produce any of the desired tosylformamide **6**. Fortunately, replacing DMF with a 1:1 mixture of toluene:acetonitrile efficiently produced the bis-formamide **7** after 5 h at 50 °C.

SCHEME 5



Addition of *p*-toluenesulfinic acid to this mixture at 50 °C for an additional 5 h produced the tosylformamide **6** in 93% isolated yield (Scheme 5). Subsequently, we found it was unnecessary to pre-form the bis-formamide **7** prior to adding the *p*-toluenesulfinic acid to the reaction mixture.

TABLE 1. Preparation of Substituted Tosylmethyl Formamides



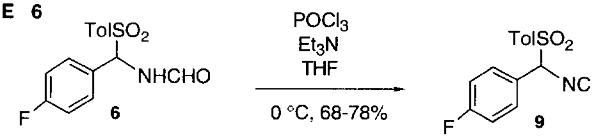
(4)

Entry	R1	R2	Product (4) yield	reaction time (h)
1	4-F-Ph	H	93%	5
2	Ph	H	94%	5
3	4-MeO-Ph	H	92%	5
4	3-Thiophene	H	81%*	5
5	t-Bu	H	70%*	6
6	Me_2CH	H	62%*	5
7	Ph	Me	88%*	5

*no attempt was made to optimize the yields of these products

Simply heating the aldehyde, formamide, TMSCl and *p*-toluenesulfinic acid in a 1:1 mixture of toluene: acetonitrile at 50 °C for 5 h produced **6** in 93% isolated yield,[12] even on a multi-kilogram scale. Table 1 shows a number of examples of this transformation. Electron-rich and electron-poor aromatic substrates, as well as benzaldehyde, worked equally well in this reaction. Likewise, thiophene-3-carboxaldehyde gave a high yield of the corresponding formamide. Both enolizable and non-enolizable aliphatic aldehydes also gave the desired product in moderate to good yields. In addition, replacing formamide with acetamide produced the expected product[4c] in high yield (Entry 7).

SCHEME 6



Finally, the straightforward dehydration of formamide **6** to the TosMIC derivative **9** was accomplished using a slight modification of the literature[6] procedure (Scheme 6). This conversion was successful even on 13.0 kg scale to yield 68% of the tan, crystalline product **9**. Despite prior concerns, these TosMIC derivatives are easily handled and have shelf-lives of > 12 months at 25 °C.

In summary, substituted TosMIC derivatives which had previously been inaccessible or available in low yields can now be obtained using this high-yielding method for the synthesis of tosylmethyl formamides followed by standard dehydration. This new method should greatly expand the utility of an already powerful synthetic tool.

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12. Typical experimental: To a 250 mL flask was added *p*-fluorobenzaldehyde (5.36 mL, 50 mmol), formamide (4.96 mL, 125 mmol), TMSCl (6.98 mL, 55 mmol), $TolSO_2H$ (11.7 g, 75 mmol), toluene (27 mL) and acetonitrile (27 mL). After heating at 50 °C for 5 h, the solution was cooled to 0 °C, 25 mL of *t*-butyl methyl ether and 100 mL of H_2O were added and stirred for 30. The solid white product **6** was filtered and dried in a vacuum oven at 40 °C (14.3 g, 93%, 99% pure by HPLC).

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