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An Efficient and Convenient Synthesis of Formamidines

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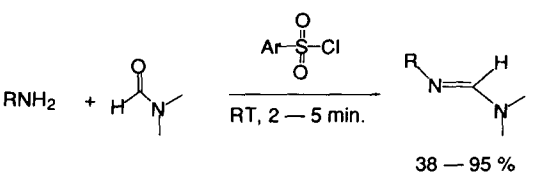
Summary: A set of new reagents, aryl sulfonyl chlorides, were used as coupling agents in the syntheses of formamidines from primary amines and N,N-dimethyl formamide in excellent yields. © 1997 Elsevier Science Ltd.

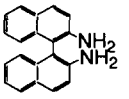
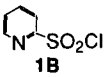
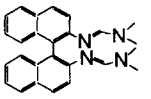
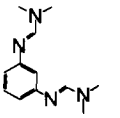
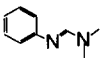
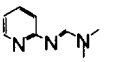
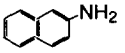
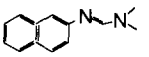
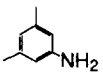
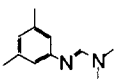
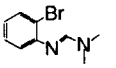
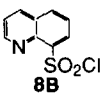
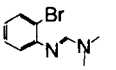
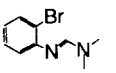
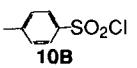
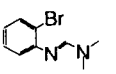
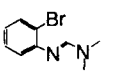
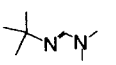
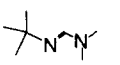
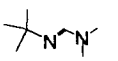
Formamidines, derivatives of the unstable imidic acid, have been used extensively as auxiliary intermediates in organic synthesis[1] and as pharmacological agents.[2] A few general methods are available for this type compounds. Coupling of N,N-dialkyl formamides with primary amines by a number of coupling agents including P_2O_5, PCl_5, PCl_3, $SOCl_2$, and acyl chlorides has been realized.[3] In other situations, ethyl N-cyanoformimidate was used to form N^2-aryl-N^1-cyanoformamidines, which were converted to a variety of N^2-aryl-N^1-alkylformamidines with excess alkyl or dialkylamines.[4] N,N-dialkylformamide dimethylacetals have also been used to couple with primary amines directly under neutral conditions.[5] Earlier phenyl isocyanate was reacted with N,N-dimethylformamide to generate formamidine through a four member heterocycle intermediate.[6] This reaction was further generalized to use other aryl isocyanates.[7] Quite unexpectedly, (diaminomethyl)di-*tert*-butylphosphine reacts with primary amines to generate formamidines and di-*tert*-butyl-hydrophosphine in moderate yields.[8] Selective reduction of tri-substituted ureas has also been used to synthesize three-substituted formamidines in a number of cases.[9] 1,1-Addition of amines to isocyanides catalyzed by AgCl at low temperature generates stereospecific isomers of formamidines, which are different from those generated by other methods.[10] In this paper, we wish to report a convenient and high efficient synthesis of a variety of formamidines by a set of new coupling agents, sulfonyl chlorides (**Eq 1**).



(1)

2-Pyridinesulfonyl chloride was synthesized according to a literature preparation with 84% isolated

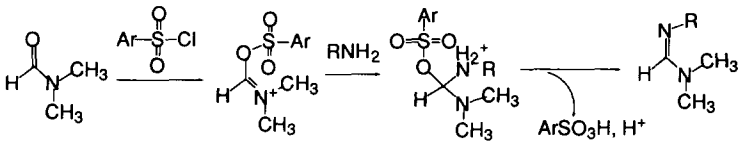
Table 1: Synthesis of Formamidines by Coupling Primary Amines with DMF.[a]

Entry	Amine		$ArSO_2Cl$	Product		Time (min.)	Yield[b] (%)
1		**1A**	 **1B**		**1C**	2—5	91
2		**2A**	**1B**		**2C**	2—5	94
3		**3A**	**1B**		**3C**	2—5	95
4		**4A**	**1B**		**4C**	2—5	87
5		**5A**	**1B**		**5C**	2—5	91
6		**6A**	**1B**		**6C**	2—5	90
7		**7A**	**1B**		**7C**	1—2	95
8		**7A**	 **8B**		**7C**	20—30	89
9		**7A**	CH_3SO_2Cl **9B**		**7C**	< 1	76[c]
10		**7A**	 **10B**		**7C**	2—5	90
11		**7A**	CH_3COCl **11B**		**7C**	2—5	< 1[d]
12	t-Bu-NH_2	**12A**	**1B**		**12C**	2—5	38[e]
13	t-Bu-NH_2	**12A**	**10B**		**12C**	2—5	< 1[d]
14	t-Bu-NH_2	**12A**	**11B**		**12C**	2—5	< 1[d]

Notes: a) All reactions were performed with 0.1 mmol of amine and 0.15 mmol of Ar-SO_2Cl in 0.5 mL DMF at RT. b) Isolated yields based on amines. All of the products were characterized by ^1H NMR, MS, and HRMS. c) A by-product, methyl sulfonyl amide, was formed. d) Pure amide was formed. No formamidine was detected by GCMS. e) 37% amide was isolated.

yield.[11] The other sulfonyl chlorides are commercially available and used as received. A typical procedure is as follows: After 1.5 eq of a sulfonyl chloride was dissolved in DMF for 5 minutes, an amine (1.0 eq) was added at room temperature. The reaction mixture was stirred for the specified time listed in **Table 1**. After the solvent was removed, K_2CO_3 solution (4M) was added. The mixture was then extracted with ether. The ether solution was dried over Na_2SO_4 and the solvent was removed to generate the pure product. The experimental conditions and isolated yields of the products are summarized in **Table 1**. Compared with the experimental conditions of 100° to 120° for P_2O_5, PCl_5, $SOCl_2$ as coupling agents, this reaction is advantageous for its mild experimental conditions, greater than about 90% yield, and short reaction times. The reactivity of 2-pyridine sulfonyl chloride and *p*-tolyl sulfonyl chloride is optimal for the synthesis of formamidines. Increasing the reactivity of the sulfonyl chloride by using methyl sulfonyl chloride increases the rate of the reaction, but decreases the yield of formamidine, and formation of sulfonyl amide is observed as shown in entry 9. Lowering the reactivity of sulfonyl chloride by using 8-quinolinesulfonyl chloride slows the reaction, although no difference in selectivity is observed. However, acyl chloride is rather poor coupling agent as shown in entries 11 and 14. 2-Pyridine sulfonyl chloride is also an effective coupling agent for diamines as shown in entries 1 and 2. Overall, anilines are better substrates than aliphatic primary amines in this reaction.

Only one isomer is observed. All unknown formamidines have been confirmed by high resolution MS and ^1H NMR. Comparison of the NMR of **3C** and **5C** with the literature assignments confirms the formation of the trans isomers. This is consistent with a thermodynamically controlled reaction. In analogous with the mechanism proposed for the formation of formamidines by other coupling agents,[3b,3c] the proposed mechanism is shown on **Scheme 1**.



Scheme 1. Possible mechanistic scheme.

In conclusion, we have described a simple, convenient, and efficient preparation of formamidines from primary amines and N,N-dimethyl formamide in the presence of sulfonyl chlorides. Its advantages lie on (a) the straightforward and simplicity of the procedure; (b) the mildness of the reaction conditions and excellent yields; and (c) short reaction time and chemoselectivity. Further studies to determine the scope, limitations, and applications of this efficient and flexible synthesis of formamidines are under active investigation and will be reported in due course.

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