Organic LETTERS

Letter

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Practical Synthesis of *N*-Substituted Cyanamides via Tiemann Rearrangement of Amidoximes

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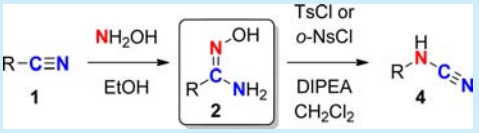
Supporting Information

ABSTRACT: A facile and general synthesis of various *N*-substituted cyanamides was accomplished by the Tiemann rearrangement of amidoximes with benzenesulfonyl chlorides (TsCl or *o*-NsCl) and DIPEA.



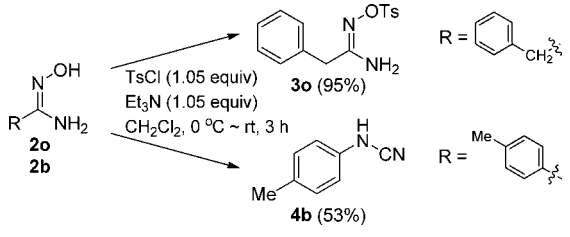
N-Substituted cyanamides have been extensively used as reactive N−C−N building blocks[1,2] and cyanating reagents in organic synthesis[3] as well as ambidentate ligands in coordination chemistry.[4] Despite their versatile applications, only a limited number of synthetic routes for *N*-substituted cyanamides have been reported in the literature.[1,2,4] The direct alkylation of cyanamide is a straightforward approach, but *N*,*N*-dialkylated cyanamides are usually obtained due to the competing alkylation of the monoalkylated cyanamides. Another common approach is the reaction of amines with BrCN, which requires caution in handling. Other approaches include dehydrosulfurization of thiourea, dehydration of urea, and the conversions from isocyanides, isocyanates, or isothiocyantes. These methods are mutually complementary since they are all originated from the corresponding amines with multistep manipulations. And some of the transformations require harsh conditions or hazardous reagents.[1,2,4]

In our attempt to prepare the *O*-tosyl amidoxime derivatives (**3**), phenylacetamidoxime (**2o**) was treated with TsCl and Et_3N in CH_2Cl_2 resulting in an excellent yield of *O*-tosyl phenylacetamidoxime (**3o**). In contrast, the reaction of *p*-toluamidoxime (**2b**) under the same reaction conditions afforded only *N*-tolylcyanamide (**4b**) in 53% yield. (Scheme 1) The rearrangement from *p*-toluamidoxime (**2b**) to *N*-tolylcyanamide (**4b**) has received our attention.

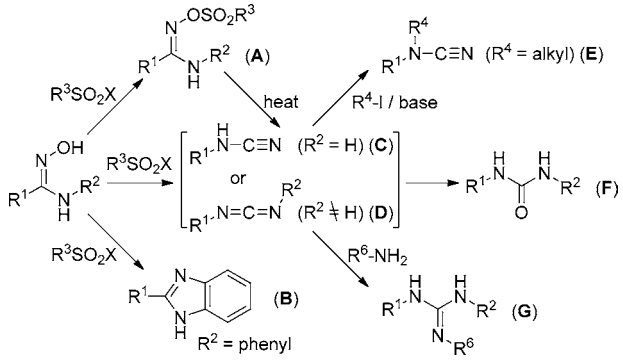
A perusal of the literature revealed that the sulfonylation of amidoximes resulted in widely diverse outcomes (summarized in Scheme 2). The reaction was dated back to 1891 when Tiemann reported the formation of *N*-phenylurea from the tolsylation of benzamidoxime, which is known as the Tiemann rearrangement.[5] *N*-Substituted cyanamides or *N*,*N*′-disubstituted carbodiimides have been shown to be the intermediates for the formation of ureas in the rearrangement.[6] They are usually accompanied by subsequent reactions to form, for instance, *N*,*N*-disubstituted cyanamides (E),[7] ureas (F),[5,6,8] or guanidines (G)[9] and can be isolated only under certain conditions (C[10] and D[11−13]). There are a few exceptions where the rearrangement did not occur after the sulfonylation of amidoximes. Some of the *O*-sulfonyl amidoximes (A) can be isolated,[8,10,11,14] and in a few cases, the *O*-sulfonyl amidoximes can proceed to the Tiemann rearrangement under thermal[10] or basic[11] conditions. Moreover, the sulfonylation of *N*-phenyl amidoximes can afford the 2-substituted benzimidazoles (B) via a nitrene intermediate,[15,16] while the Tiemann rearrangement can be excluded from the reaction.[15]

The lack of practicality due to the divergent results and indefinite scopes has limited the synthetic utilization of the Tiemann rearrangement. Thus, we embarked on the investigation of the sulfonylation of the amidoximes (**2**) to evaluate whether the Tiemann rearrangement would be a feasible

Scheme 1. Reactions of Amidoximes 2b and 2o with TsCl



Scheme 2. Divergent Results from the Sulfonylation of Amidoximes



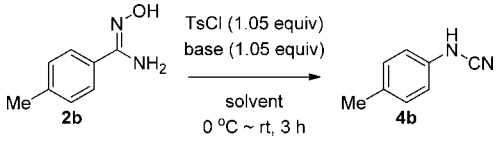
Received: December 17, 2013
Published: January 14, 2014

   dx.doi.org/10.1021/ol403645y | *Org. Lett.* 2014, 16, 892−895

approach for the preparation of a wide variety of cyanamide derivatives (**4**).

The reactions of *p*-toluamidoxime (**2b**) with TsCl under various conditions were investigated to optimize the rearrangement reaction (Table 1). The optimum conditions were to

Table 1. Optimization for the Formation of *N*-Toluylcyanamide (2b)



entry	base	solvent (0.1 M)	time (h)	yield[a] (%)
1	Et_3N	CH_2Cl_2	3	64
2	DIPEA	CH_2Cl_2	3	87
3	DBU	CH_2Cl_2	3	64
4	DABCO	CH_2Cl_2	3	82
5	Cs_2CO_3	CH_2Cl_2	3	47
6	DIPEA	MeCN	3	83
7	DIPEA	THF	3	45
8	Cs_2CO_3	MeCN	3	80
9		pyridine (1 M)	1	95

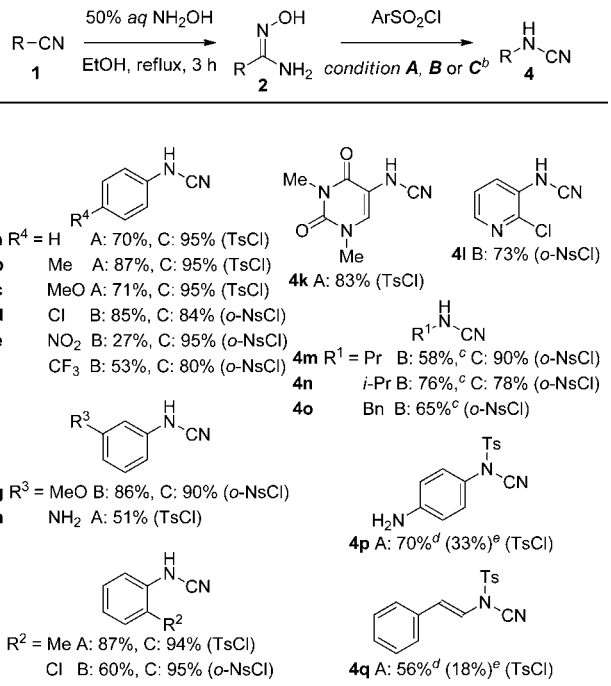
[a]Isolated yield.

carry out the reaction with 1.05 equiv of TsCl and 1.05 equiv of DIPEA in CH_2Cl_2 from 0 °C to room temperature in 3 h (entry 2 in Table 1, as conditions A). Alternatively, we also found that the yield could be substantially improved when the reaction was carried out in pyridine at ambient temperature (entry 9 in Table 1, as conditions C).

With the optimized conditions established, various amidoximes **2a**−**u**, prepared from carbonitriles **1a**−**u** with hydroxylamine, were subjected to the reaction with TsCl under conditions A in order to explore the scope and generality of the reaction. Most of the π-electron-rich aryl amidoximes (**2a**−**c**,**h**,**i**,**k**), except *m*-methoxybenzamidoxime (**2g**), can undergo the rearrangement to afford the corresponding cyanamides (**4a**−**c**,**h**,**i**,**k**) in good yields. The reactions of *p*-nitro- and *p*-trifluoromethylbenzamidoximes (**2e**,**f**), 2-chloropyridine-3-amidoxime (**2l**) as well as butyramidoxime (**2m**) resulted in the corresponding *O*-tosyl amidoximes (**3e**,**f**,**l**,**m**) as their only products, whereas the rest of the amidoximes (**2d**,**g**) gave complicated results (Scheme 3).

We postulated that the heterolytic N−O bond cleavage of the amidoximes is the driving force for the rearrangement. Thus, *o*-nitrobenzenesulfonyl chloride (*o*-NsCl) was employed instead of TsCl to provide a better leaving group, and the reaction temperature was slightly raised to the reflux temperature of CH_2Cl_2 to facilitate the rearrangement. The improved conditions allowed the rearrangement to proceed, and the corresponding cyanamides (**4**) were obtained in good yields (conditions B in Scheme 3). The reaction of the amidoximes (**2**) with TsCl or *o*-NsCl in pyridine produced the same results with even better yields (conditions C in Scheme 3). It is notable that the reaction of *p*-aminobenzamidoxime (**2p**) under conditions A gave only 33% of the isolated product, which was identified as N^1-tosylated N^1-phenylcyanamide (**4p**). Upon increasing both TsCl and DIPEA to 2.1 equiv, **4p** was obtained in 77% yield. N^1-Tosyl-N^1-phenylethenylcyanamide (**4q**) was obtained from cinnamidoxime (**2q**) under the same circumstances (Scheme 3).

Scheme 3. Preparation of N^1-Substituted Cyanamides (4) from Amidoximes (2)[a,b]



[a]Isolated yield from amidoxime **2**; [b]Conditions A: TsCl (1.05 equiv), DIPEA (1.05 equiv), CH_2Cl_2 (0.1 M), 0 °C to rt, 3 h. Conditions B: *o*-NsCl (equiv), DIPEA, CH_2Cl_2 (0.1 M), reflux, 1 h. Conditions C: $ArSO_2Cl$ (1.05 equiv), pyridine (1 M), 0 °C to rt, 0.5−12 h (monitored by TLC). [c]24 h. [d]2.1 equiv of TsCl and DIPEA. [e]1.05 equiv of TsCl and DIPEA.

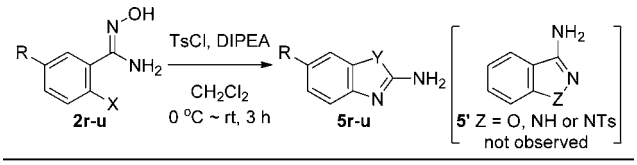
Since nitrene has been proposed as the reactive intermediate in the Tiemann rearrangement, the reactions of benzamidoximes possessing *ortho*-nucleophilic substituents were investigated, with the intent to trap the putative nitrene intermediate with the *ortho*-nucleophiles prior to the rearrangement. We anticipated that 3-amino-benzo-1,2-heteroazoles (**5′**) would be obtained if the nitrene intermediate was formed and immediately trapped by the adjacent heteroatom nucleophiles. In contrast, 2-aminobenzo-1,3-heteroazoles (**5**) would be obtained if the Tiemann rearrangement took place prior to the intramolecular nucleophilic ring closure.

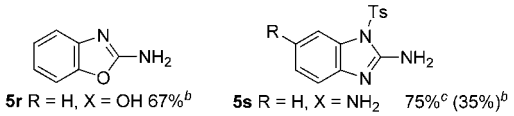
When 2-hydroxybenzamidoxime (**2r**) was treated with TsCl under conditions A, 2-aminobenzoxazole (**5r**) was obtained as the sole product in 67% yield, and its structure was confirmed by comparing the NMR spectra with the same compound previously reported in the literature.[17] Similarly, when 2-aminobenzamidoxime (**2s**) was reacted with 1.05 equiv of TsCl under conditions A, 1-tosyl-2-aminobenzimidazole (**5s**) was obtained as the only product in 35% yield, and its structure was confirmed by X-ray crystallography. The yield was increased to 75% when 2.1 equiv of TsCl and DIPEA were used. To further clarify the sequence of the tosylation and cyclization in the reaction, both 5-chloro- and 5-nitro-2-aminobenzamidoximes (**2t**,**u**) were subjected to the same conditions. The corresponding 6-substituted 1-tosyl-2-aminobenzimidazoles (**5t**,**u**) were obtained as the only products, and their structures were confirmed by X-ray crystallography. It is noticeable that the *N*-tosylation took place exclusively at the ring-nitrogen instead of the exocyclic amino group. The regiospecific tosylation was concatenated with the reaction sequence in which the

dx.doi.org/10.1021/ol403645y | Org. Lett. 2014, 16, 892−895

tosylation occurred at the N^1-position of the cyanamide prior to the cyclization (Scheme 4).

Scheme 4. Reaction of *o*-Hydroxy- and *o*-Aminobenzamidoximes (2r–u)[a]



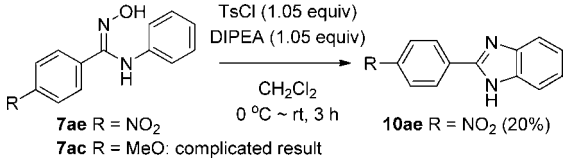


[a]Isolated yield. [b]TsCl (1.05 equiv); DIPEA (1.05 equiv). [c]TsCl (2.1 equiv); DIPEA (2.1 equiv).

The success in the synthesis of *N*-substituted cyanamides (**4**) from amidoximes (**2**) prompted us to further expand the scope of this methodology to *N*-substituted amidoxime derivatives (**7**). *N*-Substituted benzamidoxime derivatives (**7**) for our investigation were prepared from the corresponding benzaldehydes (**6**) following the literature procedure.[18] On the basis of the rearrangement of amidoximes (**2**) to cyanamides (**4**), carbodiimides (**8**) or *N*,*N*′-disubstituted ureas (**9**) would be interpreted as the products from the reaction of *N*-substituted amidoxime derivatives (**7**).

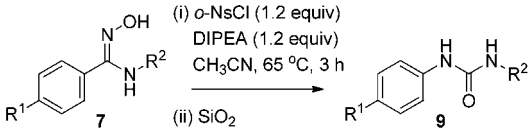
In our initial trials, *N*-phenyl 4-methoxybenzamidoxime (**7ac**) was reacted with TsCl under conditions A and the reaction gave no definite products but a complicated result. In contrast, when *N*-phenyl 4-nitrobenzamidoxime (**7ae**) was subjected to the same conditions, the only product isolated in 20% yield from the reaction was identified as 2-(4-nitrophenyl)-benzimidazole (**10ae**). The formation of the 2-substituted benzimidazoles from the *O*-tosylation of *N*-phenyl benzamidoximes has been previously documented by Partridge[16] and Yamamoto.[15] Our desired rearrangement products, either carbodiimides (**8**) or *N*,*N*′-disubstituted ureas (**9**), were not observed in both reactions (Scheme 5).

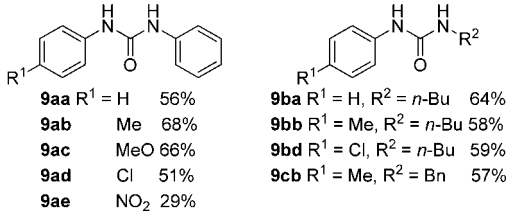
Scheme 5. Reactions of *N*-Phenylbenzamidoximes 7ac and 7ae with TsCl under Conditions A



Since the *O*-tosylation was incapable of promoting the Tiemann rearrangement, we adopted our previous strategy which employed *o*-NsCl as the sulfonylating reagent and further raised the reaction temperature to the reflux temperature of acetonitrile to facilitate the rearrangement. The reaction conditions could overcome the competing benzimidazole formation and allowed a series of *N*-substituted benzamidoximes (**7**) to undergo the Tiemann rearrangement. However, only the *N*,*N*′-disubstituted ureas (**9**), presumably hydrolyzed in situ from the carbodiimides (**8**) in the slightly acidic reaction media and silica gel column, were isolated from the reaction after several attempts (Scheme 6).

Scheme 6. Tiemann Rearrangement of *N*-Substituted Benzamidoximes (7)[a]





[a]Isolated yield.

In summary, our investigation has shown that the benzenesulfonyl chlorides promoted rearrangement of amidoximes is highly dependent on the electronic effect of the substrates.[13] Nevertheless, this survey of the reaction scope indicated that the rearrangement reaction is readily amenable for the synthesis of a wide variety of cyanamide derivatives on multigram scales from the corresponding carbonitriles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray structural data (CIF) of **4q** and **5s–u**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Research Grant Nos. 102-2113-M-003-004- and 100-2113-M-003-007-MY2 from the National Science Council, Taiwan, and NTNU100-D-06 from National Taiwan Normal University. We also thank Professor Toshio Fuchigami (Tokyo Institute of Technology) for his helpful discussions and Mr. Ting-Shen Kuo (National Taiwan Normal University) for his assistance with X-ray crystallographic analysis.

■ DEDICATION

This paper is dedicated to Professor Leroy B. Townsend on the occasion of his 80th birthday.

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