Facile One-pot Syntheses of Amidines and Enamines from Oximes via Beckmann Rearrangement Using Trifluoromethansulfonic Anhydride

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Facile one-pot syntheses of amidines and enamines were achieved by trapping carbocation intermediates that were formed by Beckmann rearrangement of oximes with amines and carbon nucleophiles, respectively, under mild conditions.

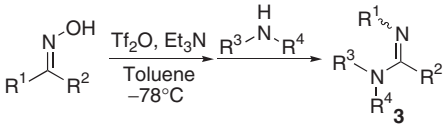
Beckmann rearrangement[1] is a well-known useful tool having a wide range of applications in organic synthesis for the construction of nitrogen-containing compounds[2] such as α-alkylated amines[3] via imines, amidines,[4] thioimidates,[5] imidoyl halides,[6] imidoyl cyanides,[5] iminophosphonates,[7] and enaminones.[8] Amidines were synthesized by trapping the iminocarbocation intermediates of Beckmann rearrangement derived from oximes,[9,10] oxime sulfonates,[4] oxime carbonates, and oxime phosphonium salts[11] with primary or secondary amines. There are also some reports on the formations of amines[3] or enamines[8] by trapping the intermediates with the carbon nucleophiles. In some cases, however, these reported procedures require isolation of oxime sulfonates or high reaction temperature, and products yields are low. Then, it was considered that if the oximes having a strong leaving group such as trifluoromethanesulfonate were to be used, Beckmann rearrangement would proceed smoothly under milder conditions to provide a convenient procedure. Among the Beckmann type reactions of ketoximes that form nitriles, dehydrated products, or the rearranged products of common amides by the use of trifluoromethanesulfonic anhydride,[12] no reaction that traps the iminocarbocation intermediates with amines or carbon nucleophiles is known.

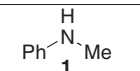
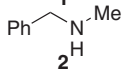
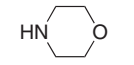
Here, we would like to report facile one-pot syntheses of amidines and enamines under mild conditions by trapping the intermediates, generated from oximes by Beckmann rearrangement, with amines or carbon nucleophiles.

In the first place, the carbocation intermediate of Beckmann rearrangement generated from benzophenone oxime and trifluoromethanesulfonic anhydride was studied to see if it was trapped by *N*-methylaniline. The carbocation intermediate was generated by adding trifluoromethanesulfonic anhydride to the toluene solution of benzophenone oxime and triethylamine at $-78\,^{\circ}$C. Then, *N*-methylaniline was added to the reaction mixture and was warmed up to room temperature. After aqueous work up, the desired product was obtained in 95% yield. Various amidines were similarly prepared by the above-mentioned one-pot procedure from the corresponding oximes. For example, treatment of aromatic oximes with aromatic or aliphatic amines gave the corresponding amidines in good yields (Table 1, Entries 1–5). The reactions proceeded smoothly also in the case of less reactive aliphatic oximes and gave the desired products in high yields (Entries 6–8). According to this procedure, the yield of rearranged product of cyclic oxime was improved compared with that by the ordinary method[4] (Entry 9).

Next, the trapping of iminocarbocation intermediates with carbon nucleophiles was tried. The reaction was thought to provide a new method for the formation of enamines by one-pot procedure: namely, Beckmann rearrangement of oximes to form iminocarbocations and successive reaction of thus formed carbocations with carbon nucleophiles afforded the enamines under mild conditions. A similar example was reported by Yamamoto and co-workers, in which enaminones[8] were obtained from oxime sulfonates and enol silyl ethers in the presence of Lewis acid such as diethylaluminum chloride.

Table 1. Syntheses of amidines by trapping with amines



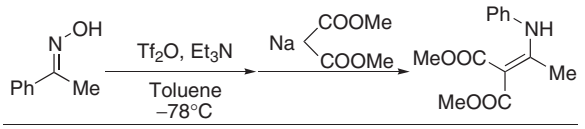
Entry	R^1	R^2	$R^3{-}N(H){-}R^4$	Product	Yield /%[a,b]
1	Ph	Ph	 **1**	**3a**	95[c]
2			 **2**	**3b**	99
3				**3c**	87
4	Ph	Me	**1**	**3d**	89
5			**2**	**3e**	86
6	Me	Me	**1**	**3f**	93
7	Et	Et	**1**	**3g**	99
8			**2**	**3h**	99
9	$-(CH_2)_5-$		**1**	**3i**	83

[a]Isolated yield. [b]All products were obtained as a single isomer and the geometry of them were not determined. [c]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroetahne as an internal standard.

The reactions of acetophenone oxime and sodium methylmalonate were tried as the model. It was revealed that at least 3.0 equivalents of nucleophile were necessary in order to obtain the desired product in high yield (Table 2, Entry 3).

The reaction was further examined by using various aromatic and aliphatic oximes (Table 3 Entries 1–5), and it became clear that all the reactions proceeded smoothly to afford the corresponding enamines in good to high yields. It was considered that thus obtained enamines derived from aromatic oximes would be converted to 2-substituted 4-oxo-3-qunorinecarboxylic acid derivatives[13] which possess antibacterial activities by subsequent intramolecular Friedel–Crafts acylation.[14] Similar reactions using other nucleophiles were further studied and a mixture of *C*- and *O*-alkylated products was obtained in 94% yield in the case using sodium enolate of β-ketoester as a nucleophile (Entry 7). When sodium enolate of methyl cyanoacetate was used together with two ketoximes, respective reactions gave only one product in high yields (Entries 8 and 9). Furthermore, phenylsulfonylacetonitrile was also used as a nucleophile together with DBU, a base, and the corresponding product was obtained in 72% yield (Entry 10). On the other hand,

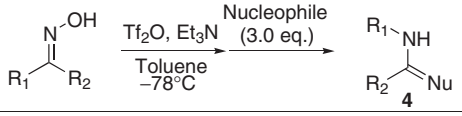
Table 2. The effect of yields on the amount of nucleophile



Entry	Nucleophile	Equivalent	Yield /%[a]
1	Na(COOMe)(COOMe)	1.5	3[b]
2	Na(COOMe)(COOMe)	2.0	41
3	Na(COOMe)(COOMe)	3.0	96

[a]Isolated yields. [b]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroetahne as an internal standard.

Table 3. Syntheses of enamines by trapping with carbon nucleophiles



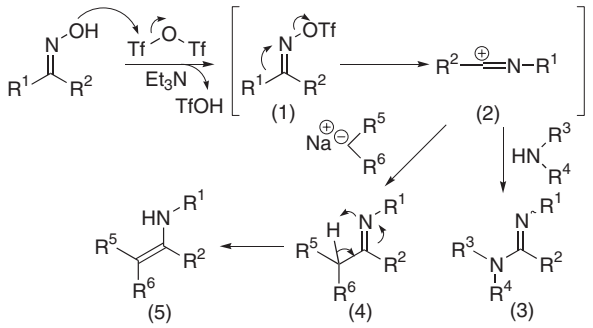
Entry	R_1	R_2	Nu	Product		Yield /%[a]
1	Ph	Me	Na(COOMe)(COOMe)	R1 NH, R2, COOMe, COOMe	**4a**	96
2	4-MeOPh	Me			**4b**	95
3	4-NO_2Ph	Me			**4c**	95
4	Ph	Ph			**4d**	81
5	Me	Me			**4e**	78
6	Et	Et			**4f**	73
7	Ph	Me	Na(COMe)(COOEt)	Ph NH, Me, COMe, COOEt / Ph N, Me O, COOEt	**4g** **4h**	94[b]
8	Ph	Me	Na(CN)(COOMe)	R1 NH, R2, COOMe, CN	**4i**	99
9	Me	Me			**4j**	99
10	Me	Me	DBU SO2Ph CN	Me NH, Me, SO2Ph, CN	**4k**	72
11	Ph	Me	Na(PO(OEt)2)(CN)	Ph NH, Me, PO(OEt)2, CN	**4l**	50
12	Me	Me	ONa, Ph	Me NH, O, Ph, Me	**4m**	18 30[c] 30[d]

[a]Isolated yields. [b]The proportion of product was C(**4g**)/O(**4h**)=71/29. [c]4 equiv. of nucleophile was used. [d]5 equiv. of nucleophile was used.

the desired product was obtained in low yield when sodium enolate of acetophenone was used as a nucleophile (Entry 12).

A proposed reaction mechanism is shown in Scheme 1. Initially, the oxime is activated with trifluoromethansulfonic anhydride to form a reactive oxime trifluoromethanesulfonate (**1**). The successive elimination of triflate anion from (**1**) caused rearrangement of R^1 to nitrogen atom to afford iminocarbocation (**2**), which in turn was trapped with secondary amine to give the corresponding amidine (**3**), or the imine (**4**) when treated with carbon nucleophile such as a sodium malonate. Thus produced imine (**4**) was converted to enamine (**5**) via 1,3-proton-shift.

A typical experimental procedure is as follows: to a solution of acetoxime (0.25 mmol) and triethylamine (0.50 mmol) was added a



Scheme 1.

trifluoromethanesulfonic anhydride (0.38 mmol) in toluene (3.0 mL) under an argon atmosphere at −78 °C. After stirring for 5 min, freshly prepared sodium salt of methyl malonate dissolved in THF (0.3 M, 2.5 mL) was added and the reaction mixture was slowly warmed up to room temperature. After stirring for 1 h, the reaction mixture was quenched with water (5.0 mL) and the aqueous layer was extracted with ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), filtrated and evaporated, and the resulted residue was purified by preparative TLC to afford the corresponding product.

Thus, a new and efficient method for the one-pot syntheses of amidines and enamines was established by trapping iminocarbocation intermediates generated via Beckmann rearrangement of ketoximes with trifluoromethansulphonic anhydride, with amines and carbon nucleophiles, respectively, without using Lewis acid under mild conditions. Further study on this type of reaction is currently in progress.

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References

1 a) E. Becmann, *Ber.*, **19**, 988 (1886). b) E. Beckmann, *Ber.*, **20**, 1507 (1887).
2 a) I. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960). b) C. G. MaCarty, in "Chemistry of the Carbon-Nitrogen Double Bond," ed. by S. Patani, Wiley-Interscience, New York (1970), p 408.
3 a) K. Hattori, Y. Matsumura, T. Miyazaki, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **103**, 7368 (1981). b) K. Hattori, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **23**, 3395 (1982).
4 P. Oxley and W. F. Short, *J. Chem. Soc.*, **1948**, 1514.
5 K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 2831 (1983).
6 Y. Ishida, S. Sasatani, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **24**, 3255 (1983).
7 T. Yokomatsu, T. Minowa, Y. Yoshida, and S. Shibuya, *Heterosycles*, **44**, 111 (1997).
8 Y. Matsumura, J. Fujiwara, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 6312 (1983).
9 A. R. Katrizky, D. A. Monteux, and D. O. Tymoshenko, *Org. Lett.*, **4**, 577 (1999).
10 J. T. Gupton, J. P. Idoux, R. Leonard, and G. DeCrescenzo, *Synth. Commun.*, **13**, 1083 (1983).
11 S. Teidebaut, C. Gerardin-Charbonnier, and C. Selve, *Tetrahedron*, **55**, 1329 (1999).
12 a) G. A. Olah, Y. D. Vankar, and A. L. Berrier, *Synthsis*, **1980**, 45. b) A. G. Martínes, E. T. Vilar, A. G. Fraile, S. de la Moya Cerero, C. D. Oliva, L. R. Subramanian, and C. Maichle, *Tetrahedron: Asymmetry*, **5**, 949 (1994).
13 C. Mitsos, A. Zografos, and O. Igglessi-Markopoulou, *Chem. Pharm. Bull.*, **48**, 211 (2000).
14 a) K. Umeyama, O. Morimoto, and P. Yamashita, *Tetrahedron Lett.*, **30**, 4821 (1989). b) O. Hormi, C. Peltonen, and L. Heikkila, *J. Org. Chem.*, **55**, 2513 (1990).

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