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Application of α-chloroaldoxime *O*-methanesulfonates to one-pot synthesis of *N*,*N*′,*N*″-substituted guanidines via Tiemann rearrangement

Yuhei Yamamoto *, Hiroo Mizuno, Takayuki Tsuritani, Toshiaki Mase

Process Research, Preclinical Development, Banyu Pharmaceutical Co., Ltd, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan

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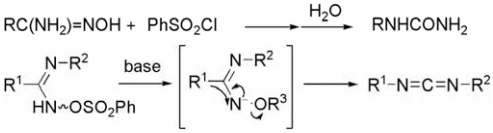
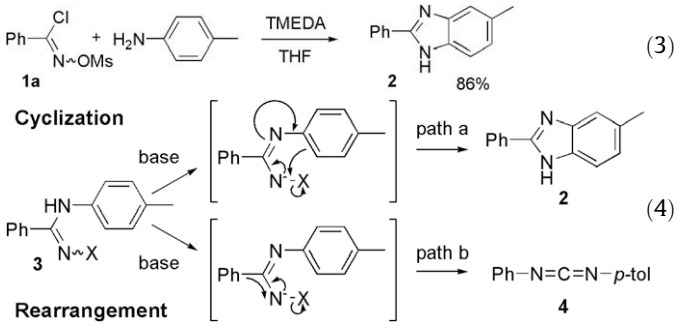
ABSTRACT

A practical one-pot synthesis of *N*,*N*′,*N*″-trisubstituted guanidines via Tiemann rearrangement involving the reaction of α-chloroaldoxime *O*-methanesulfonates with alkyl amines is disclosed.

The Tiemann rearrangement, the aza analogue of the Lossen rearrangement, was originally reported for conversion of amidoximes to ureas (Eq. 1).[1,2] The primary product of the reaction is the amidoxime *O*-benzenesulfonate, which then rearranges to give a carbodiimide (Eq. 2).[3] Although this rearrangement provides an efficient pathway to carbodiimides, which are versatile synthetic intermediates,[4] only a few synthetic applications of this potentially useful reaction have appeared in the literature.[1,3,5]



Recently, we disclosed a benzimidazole synthesis using α-chloroaldoxime *O*-methanesulfonate **1** (Eq. 3) as the key starting material.[6] The reaction proceeds via amidoxime *O*-methansulfonate **3** (X = OMs) which immediately cyclizes to give benzimidazole **2** (Eq. 4), path a).[7] Although the amidoxime intermediate **3** could also potentially undergo the Tiemann rearrangement (Eq. 4, path b), no trace of carbodiimide was observed throughout the reaction. Consistent with literature reports, this observation may be attributed to the nature of the leaving group on the amidine nitrogen.[7g] The cyclization (path a) is generally preferred for amidines bearing moderate leaving groups such as Cl,[7b,7e] and the rearrangement (path b) is preferred for amidines bearing exceptionally good leaving groups such as N_2^+ and I^+Ph.[7a,7f] Independent of the nature of the leaving group, it seemed reasonable to expect the rearrangement pathway (path b) to predominate when the substituent on the amidine nitrogen was an alkyl group (R^2=alkyl) which is unable to cyclize. Herein we wish to report a novel one-pot synthesis of *N*,*N*′,*N*″-trisubstituted guanidines via Tiemann rearrangement involving the reaction of α-chloroaldoxime *O*-methanesulfonates **1** with alkyl amines.



We initiated our investigation using *N*-benzylethylenediamine as the alkyl amine to react with various α-chloroaldoxime methanesulfonates (Table 1). The reaction should initially give the amidoxime *O*-methanesulfonate **3**. If the rearrangement takes place, the amidoxime *O*-methanesulfonate **3** would convert to the carbodiimide which could then be intramolecularly trapped with the benzylamine moiety to produce the cyclic guanidine.[8] Four different α-chloroaldoxime methanesulfonates **1a–d** were employed to react with *N*-benzylethylenediamine, and the results are summarized in Table 1. The reaction of α-chlorobenzaldoxime methanesulfonate **1a** with *N*-benzylethylenediamine completed at room temperature,

* Corresponding author. Tel./fax: +81 6 6300 6251.
E-mail addresses: yuhei_yamamoto@merck.com, Yamamoto_Yuuhei@takeda.co.jp (Y. Yamamoto).

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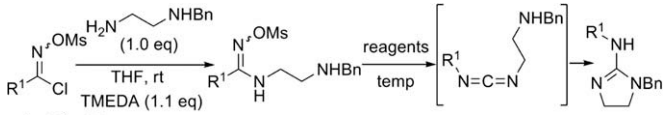
Table 1
Reaction of various α-chloroaldoxime methanesulfonates with *N*-benzylethylenediamine



1a: R^1 = Ph **3a-d** **4a-d** **5a-d**
1b: R^1 = 2-chlorophenyl
1c: R^1 = 2-pyridyl
1d: R^1 = 3-nitrophenyl

Entry	Substrate	Reagents	Temp (°C)	Yield (%)	
				3	**5**
1	**1a**	None	rt	<1	96
2	**1b**	None	70	<5	87
3	**1c**	None	rt	97	<1
4	**1c**	None	70	<5	<5
5	**1c**	DBU (2.4 equiv)/DMF	rt	<1	89
6	**1d**	None	rt	98	<1
7	**1d**	None	70	<5	<5
8	**1d**	DBU (2.4 equiv)/DMF	rt	<5	<5

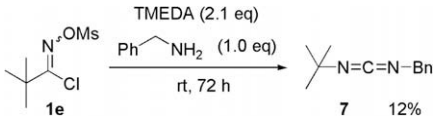
and gave the cyclic guanidine **5a** in 96% yield (entry 1). The starting materials and the cyclic guanidine were the only observed compounds during the reaction, and no trace of amidoxime *O*-methanesulfonate **3a** was observed. In contrast, the reaction of 2-chlorophenyl substituted α-chloroaldoxime methanesulfonate **1b** did not give the cyclic guanidine **5b** at room temperature. Although we were not able to isolate the compound, the reaction seemed to stall at the amidoxime *O*-methansulfonate **3b**.[9] The desired cyclic guanidine **5b** was obtained when the reaction mixture was heated to 70 °C (entry 2). When the reaction was conducted with α-chloroaldoxime methanesulfonates bearing electron-withdrawing groups such as 2-pyridyl (**1c**) and 3-nitrophenyl (**1d**), we were able to isolate the amidoxime intermediates **3c** (entry 3) and **3d** (entry 6). In contrast to 2-chlorophenyl-substituted amidoxime **3b**, both compounds **3c** and **3d** decomposed when the reaction mixtures were heated (entries 4 and 7). The desired cyclic guanidine **5c** was obtained for 2-pyridyl-substituted amidoxime **3c** when DBU (2.4 equiv) was added into the reaction mixture (entry 5),[10] but only decomposition occurred when DBU was added to the 3-nitrophenyl-substituted amidoxime **3d** (entry 8).

From these results, it is clear that the electron density of the R^1 substituent plays a crucial role on the reaction. Electron deficient R^1 groups facilitate the first step to form amidoximes **3a–d**, but inhibit the migration. It is interesting to note that the reaction conditions that affect the migration can be categorized into four types, depending on the electron density of the R^1 substituent.[5c] Thus, the phenyl group migrated at room temperature, but the 2-chlorophenyl group required heat to induce the migration. The 2-pyridyl group required strong base such as DBU to migrate, but the 3-nitrophenyl group did not migrate even with DBU under forcing conditions. The trend in migratory aptitudes is somewhat analogous to that of Lossen rearrangement,[11] but the reaction mechanism in the present case is not clear at this time.

We next turned our attention to the synthesis of various *N*,*N*′,*N*″-trisubstituted guanidines,[12] as such compounds are found in a number of biologically active compounds and asymmetric reagents.[13,14] The present method enables the one-pot synthesis of *N*,*N*′,*N*″-trisubstituted guanidines by sequential addition of alkyl amines to α-chloroaldoxime methanesulfonates. The results of these studies are summarized in Table 2.

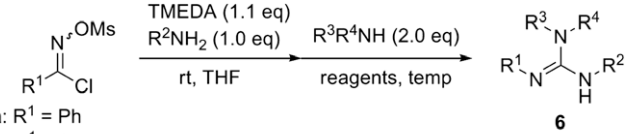
The reaction conditions used for the one-pot synthesis are basically the same as those used for the synthesis of cyclic guanidines (**5a–c**), except for the temperature of the reaction with the second amine. For example, the reaction of phenyl-substituted α-chloroaldoxime methanesulfonate **1a** with amines completed at room temperature to give the corresponding carbodiimides, but the reaction of the intermediate carbodiimides with a second series of amines did not proceed until the mixture was heated to 50 °C (entries 1–5).[15] The reaction of 2-chlorophenyl-substituted α-chloroaldoxime methanesulfonate **1b** gave the corresponding amidoxime at room temperature, and was heated to 70 °C after the addition of second amine to give the desired guanidines in moderate yield (entries 6 and 7).[16] The reaction of 2-pyridyl-substituted α-chloroaldoxime methanesulfonate **1c** with primary amines immediately gave the corresponding amidoximes at room temperature. The desired guanidine was obtained after addition of second amine and DBU with heating (entries 8–11).[17]

The rearrangement was not limited only to aryl-substituted α-chloroaldoxime methanesulfonates. The reaction also proceeds with the ^{t}Bu-substituted α-chloroaldoxime methanesulfonate **1e** to give the corresponding carbodiimide (Eq. 5), albeit in low yield.[18] The low yield is attributed to the low reactivity of the substrate **1e** caused by its steric bulk.[6a]



(5)

Table 2
One-pot synthesis of various *N*,*N*′,*N*″-substituted guanidines



1a: R^1 = Ph
1b: R^1 = 2-chlorophenyl
1c: R^1 = 2-pyridyl

Entry	Substrate	R^2	R^3, R^4	Reagents	Temp (°C)	Yield (%)
1	**1a**	^{i}Pr	^{i}Pr, H	None	50	91
2	**1a**	Bn	Bn, H	None	50	93
3	**1a**	1,2,2-Trimethylpropyl	1,2,2-Trimethylpropyl, H	None	50	95
4	**1a**	Bn	^{n}Bu, H	None	50	86
5	**1a**	Bn	–$(CH_2)_4$–	None	50	91
6	**1b**	Bn	–$(CH_2)_4$–	None	70	71
7	**1b**	Bn	–$(CH_2CH_2OCH_2CH_2)$–	None	70	79
8	**1c**	^{n}Bu	Bn, H	DBU/DMF	35	87
9	**1c**	Bn	–$(CH_2)_4$–	DBU/DMF	35	88
10	**1c**	^{i}Pr	–$(CH_2)_4$–	DBU/DMF	35	91
11	**1c**	^{t}Bu	–$(CH_2)_4$–	DBU/DMF	35	87

Further elucidating the mechanism of the rearrangement and expanding the range of substrates are ongoing in our laboratory.

Acknowledgments

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15. Synthesis of *N*,*N*′,*N*″-substituted guanidines from α-chlorobenzaldoxime *O*-methanesulfonate (**1a**) (Table 2, entry 4): To 50 mL round flask were added benzylamine (214 mg, 2 mmol), α-chlorobenzaldoxime *O*-methanesulfonate **1a** (467 mg, 2.0 mmol), THF (10 mL), and TMEDA (256 mg, 2.2 mmol). The solution was stirred at room temperature for 5 h. *n*-Butylamine (292 mg, 4 mmol) was added to the reaction mixture, and the mixture was warmed to 50 °C. The reaction mixture was stirred at the same temperature for additional 5 h, and the reaction mixture was directly purified through SiO_2 column to give the desired guanidine as yellow oil (484 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.34 (m, 4H), 7.31–7.25 (m, 3H), 6.95 (tt, J = 7.2, 1.2 Hz, 1H), 6.92 (dd, J = 8.0, 1.2 Hz, 2H), 4.39 (s, 2H), 4.21 (br s, 1H), 3.77 (br s, 1H), 3.12 (m, 2H), 1.44 (tt, J = 7.2, 7.2 Hz, 2H), 1.26 (tq, J = 7.2, 7.2 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 150.0, 139.1, 129.3, 128.7, 127.4, 127.4, 123.6, 121.6, 46.1, 41.7, 31.8, 20.0, 13.8; IR (neat, cm^{-1}) 2956, 2926, 2861, 1615, 1584, 1516, 1483, 1264, 1135, 1069, 731, 695; HRMS m/z calcd for $C_{18}H_{24}N_3$: 282.1970; Found: 282.1970.
16. Synthesis of *N*,*N*′,*N*″-substituted guanidine from α-chloro(2-chlorophenyl)-benzaldoxime *O*-methanesulfonate (**1b**) (Table 2 entry 6): To 50 mL round flask were added benzylamine (214 mg, 2.0 mmol), α-chloro(2-chlorophenyl)-carboxaldoxime *O*-methanesulfonate **1b** (536 mg, 2.0 mmol), THF (10 mL), and TMEDA (256 mg, 2.2 mmol). The solution was stirred at room temperature for 5 h. Pyrrolidine (280 mg, 4 mmol) was added to the reaction mixture, and the mixture was warmed to 70 °C. The reaction mixture was stirred at the same temperature for additional 5 h, and the reaction mixture was directly purified through SiO_2 column to give the desired guanidine as yellow oil (446 mg, 71% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.32 (m, 4H), 7.30–7.26 (m, 2H), 7.07 (td, J = 7.6, 1.6 Hz, 1H), 6.89 (dd, J = 8.0, 1.6 Hz, 1H), 6.76 (td, J = 8.0, 1.6 Hz, 1H), 4.36 (s, 2H), 3.27–3.23 (m, 4H), 1.85–1.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 139.4, 129.2, 128.6, 127.8, 127.3, 127.0, 124.3, 120.7, 47.9, 47.7, 25.5; IR (neat, cm^{-1}) 2966, 2869, 1597, 1568, 1511, 1466, 1351, 1029, 745, 697; HRMS m/z calcd for $C_{18}H_{21}N_3Cl$: 314.1424; found: 314.1429.
17. Synthesis of *N*,*N*′,*N*″-substituted guanidine from α-chloro(2-pyridyl)-carboxaldoxime *O*-methanesulfonate (**1c**) (Table 2, entry 8): To 50 mL round flask were added α-chloro(2-pyridyl)carboxaldoxime *O*-methanesulfonate **1c** (469 mg, 2.0 mmol), THF (10 mL), and TMEDA (256 mg, 2.2 mmol). The mixture was cooled to 0 °C, and *n*-butylamine (146 mg, 2.0 mmol) was added to the mixture. The mixture was warmed to room temperature, and was stirred at the same temperature for 30 min. Benzylamine (428 mg, 2.0 mmol), DMF (5 mL), and DBU (731 mg, 4.8 mmol) were added to the mixture, and the mixture was stirred at 35 °C for 5 h. The reaction mixture was directly purified through SiO_2 column to give the desired guanidine as a white crystal (446 mg, 87% yield, mp 78 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (ddd, J = 5.2, 2.0, 0.8 Hz, 1H), 7.45 (ddd, J = 9.2, 7.2, 2.4 Hz, 1H), 7.40–7.33 (m, 4H), 7.31–7.26 (m, 1H), 6.89 (d, J = 9.2 Hz, 1H), 6.66 (ddd, J = 7.2, 5.2, 0.8 Hz, 1H), 4.56 (s, 2H), 3.23 (br s, 2H), 1.54 (tt, J = 7.6, 7.6 Hz, 2H), 1.33 (tq, J = 7.6, 7.6 Hz, 2H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 155.4, 145.3, 139.1, 136.9, 128.7, 127.4, 127.3, 120.2, 114.4, 45.3, 40.9, 31.6, 20.1, 13.7; IR (neat, cm^{-1}) 2953, 1558, 1506, 1429, 1355, 1147, 784, 730; HRMS m/z calcd for $C_{17}H_{23}N_4$: 283.1923; found: 283.1930.
18. ^{t}Bu-substituted α-chloroaldoxime methanesulfonate **1e** was the only example bearing aliphatic substituent that Tiemann rearrangement proceeded. The reaction of cyclohexyl or ^{n}Bu-substituted α-chloroaldoxime methanesulfonate with benzylamine gave only the corresponding amidoxime *O*-methanesulfonate, and no rearrangement occurred under our reaction conditions.