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Synthesis of Hydroximoyl Chlorides from Aldoximes and Benzyltrimethylammonium Tetrachloroiodate (BTMA ICl_4)

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Abstract—Benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) acts as a convenient reagent to convert aldoximes to hydroximoyl chlorides by a simple procedure. When an aldoxime is treated with BTMA ICl_4 in dichloromethane, the suspension of BTMA ICl_4 shortly diasappears as the reaction proceeds. The resulting BTMA ICl_2 can be precipitated out by adding diethyl ether. Not only stable aromatic and heteroaromatic hydroximoyl chlorides can be isolated by this method but also rather unstable aliphatic hydroximoyl chlorides can be generated in situ. 1,3-Dipole trapping with a dipolarophile is performed in one flask and in some cases the chlorination is successfully performed in the presence of dipolarophile and triethylamine. Effect of MS 4A has been examined.

Nitrile oxides are known to be one of the most reactive 1,3-dipoles. With alkene dipolarophiles, substituted 2-isoxazolines are produced with the retention of stereochemistry of the starting alkenes,[1] and high synthetic potential of 2-isoxazoline heterocycles is well known.[2] Nitrile oxides undergo smooth and regioselective cycloaddition reactions especially with monosubstituted alkenes, the reactivity not sensitively depending upon the electronic nature of the substituent. However, reactions with alkenes having more than one substituent are less useful where neither regioselectivity nor reactivity is satisfactory. We have recently discovered a highly regio- and *syn*-selective nitrile oxide cycloaddition reaction to allylic alcohols in the presence of magnesium ions.[3] High rate acceleration has been achieved so that this methodology may be especially useful for transformation of alkenes to 2-isoxazolines. A chelation transition structure in which nitrile oxides and allylic alcohols coordinate to the same magnesium ion is certainly responsible for the observed rate acceleration and selectivities. Presence of coordinating additive and/or solvent in the reaction mixture makes the reaction less effective. Therefore, the in situ generation methods of nitrile oxides, e.g. oxidation of aldoximes with aqueous solution of hypochlorite, should not be suitable for the magnesium ion catalyzed nitrile oxide methodology.

Benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) is quite a new chlorinating reagent regarded as 'solidified chlorine' which was first developed by Kajigaeshi and Kakinami.[4] This reagent, BTMA ICl_4, has been successfully utilized in the electrophilic chlorination of aromatic and heteroaromatic rings, benzylic chlorination of alkylbenzenes, and mono- and dichlorination of methyl ketones.[4c] Although it is a yellow solid with high stability and safe-to-store chlorinating agent, BTMA ICl_4 decomposes upon heating at around 100°C to give BTMA ICl_2 with the quantitative release of chlorine. Therefore, BTMA ICl_4 can be expected to feed chlorine slowly in reactions of aldoximes to act as a convenient chlorinating agent.

Chlorination of aldoximes leads to hydroximoyl chlorides, which are then dehydrochlorinated with triethylamine to generate nitrile oxides. One difficulty often encountered in this hydroximoyl chloride preparation is overchlorination, especially when the starting aldoximes are carrying substituents that are labile for chlorination. In such a case, a solid chlorinating agent such as BTMA ICl_4 may be conveniently utilized since (1) it is easy to weigh accurately the required amount of chlorinating agent. Over reaction should be effectively avoided. (2) BTMA ICl_4 is hardly soluble in dichloromethane, but BTMA ICl_2 is quite soluble in the same solvent, indicating that the completion of reaction can be readily estimated. (3) The product BTMA ICl_2 is hardly soluble in diethyl ether so that the hydroximoyl chloride can be separated and isolated simply by diluting

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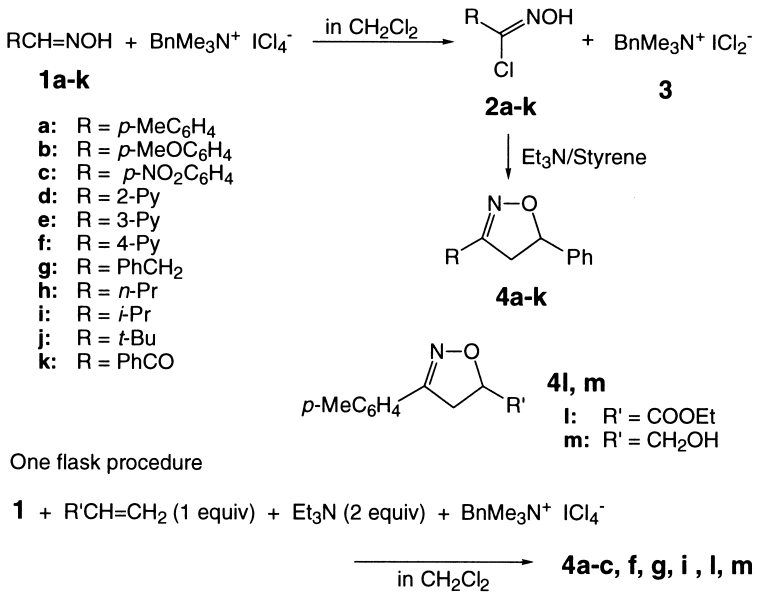


Scheme 1.

the reaction mixture with diethyl ether. However, to the best of our knowledge, this reagent has not been utilized so far in the in situ generation of nitrile oxides or in the preparation of nitrile oxide precursors, hydroximoyl chlorides.

In the present paper, we present the convenient preparation method of hydroximoyl chlorides from aldoximes and benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4). One flask procedure using styrene as dipolarophile and triethylamine leads to direct formation of isoxazolines.

(*E*)-*p*-Methylbenzaldehyde oxime (*E*-**1a**) was treated with an equimolar amount of BTMA ICl_4 in dichloromethane at room temperature. Since BTMA ICl_4 is hardly soluble in dichloromethane, this reaction becomes heterogeneous at the starting point of the reaction. However, an exothermic reaction takes place rapidly and the greenish suspension of BTMA ICl_4 dissolves into a clear yellow solution in 10 min. After stirring was continued for a few hours to confirm the completion of reaction, the solution was diluted with diethyl ether to form a precipitate of BTMA ICl_4 (**3**) as a side product which was then removed by filtration. Evaporation of the ether filtrate in vacuo gave almost pure *p*-methylbenzohydroximoyl chloride in 95% yield (Scheme 1 and Table 1). Use of *E*,*Z*-mixture of **1a** led to a comparable result, indicating the separation of each diastereomer is not necessary.[5] Other aromatic aldoximes **1b**,**c** gave the corresponding hydroximoyl chlorides **2b**,**c** in high yields.

Table 1. BTMA ICl_4 chlorination of aromatic aldoximes leading to hydroximoyl chlorides

Entry	R	Temp. (°C)	Time (h)	Product	Yield (%)
1	*p*-MeC_6H_4	rt	2	**2a**	95
2[a]	*p*-MeC_6H_4	rt	2	**2a**	Quant
3	*p*-$MeOC_6H_4$	rt	3.5	**2b**	95
4	*p*-$NO_2C_6H_4$	rt	5	**2c**	90

[a] In the presence of MS 4A (500 mg for 1 mmol scale of reaction).

Aliphatic hydroximoyl chlorides **2** (R: aliphatic) are known to be less stable in general than aromatic derivatives **2** (R: aromatic). We thought that isolation, and also purification, of aliphatic hydroximoyl chlorides should be avoided due to undesired decomposition during the isolation and/or purification procedures. Therefore, after the removal of **3** by precipitation with diethyl ether followed by filtration, the ether filtrate was evaporated in vacuo below room temperature. The residue containing hydroximoyl chlorides **2** was dissolved in dichloromethane and immediately used in the subsequent cycloaddition reaction steps. As an example, phenylacetaldehyde oxime (**1g**) was converted into the corresponding hydroximoyl chloride **2g**, the ether solvent was replaced with dichloromethane by the above procedure, and then treated with styrene (1 equiv) and triethylamine (1 equiv). Cycloaddition at room temperature took a few hours to give 3-benzyl-5-phenyl-2-isoxazoline (**4g**) in 65% yield. It should be noted that in the reaction of aliphatic aldoximes such as **1g** a prolonged reaction time in the chlorination stage decreases the yield of hydroximoyl chlorides such as **2g**. 5–10 min at room temperature would be appropriate.

A variety of aromatic (entries 1–5), heteroaromatic (entries 6–8), aliphatic (entries 9–15), and an acyl-substituted aldoxime (entry 16) were successfully converted into the corresponding nitrile oxides **2a**–**k** which were trapped with styrene as cycloadducts (Table 2). When a small excess of BTMA ICl_4 was used in the reaction of **1a**, the styrene cycloadduct **4a** was quantitatively produced. Yields of the styrene cycloadducts **4a**–**k** by this method (Method A) are satisfactory for the three step transformations including chlorination of aldoximes, nitrile oxide generation and cycloaddition to styrene. Regardless of the kinds of starting aldoximes, yields of the styrene cycloadducts are comparable, indicating the wide synthetic versatility of this nitrile oxide preparation method from a variety of aldoximes. If expensive aldoximes are employed, a small excess of BTMA ICl_4 should be utilized. However, use of excess

Table 2. Nitrile oxide generations and styrene cycloadditions by Methods A and B (equimolar amounts of BTMA ICl_4 and aldoximes were used unless otherwise noted)

Entry	R of aldoxime	Conditions of chlorination			Method A[a] yield[b] (%)	Method B[c] yield[b] (%)
		Temp (°C)	Time	Product		
1	*p*-MeC_6H_4	rt	30 min	**4a**	63	62
2	*p*-MeC_6H_4	reflux	2 h	**4a**	72	75
3	*p*-MeC_6H_4[d]	rt	2 h	**4a**	Quant	
4	*p*-$MeOC_6H_4$	rt	3.5 h	**4b**	65	
5	*p*-$NO_2C_6H_4$	rt	5 h	**4c**	60	
6	2-Py	rt	5 h	**4d**	77	
7	3-Py	rt	6 h	**4e**	67	
8	4-Py	rt	6 h	**4f**	66	
9	$PhCH_2$	rt	15 min	**4g**	65	72
10	$PhCH_2$	rt	30 min	**4g**	52	
11	$PhCH_2$[e]	rt	5 min	**4g**	70	
12	*n*-Pr	rt	15 min	**4h**		58
13	*i*-Pr	rt	1 h	**4i**	57	60
14	*t*-Bu	rt	0.5 h	**4j**	70	
15	*t*-Bu	rt	1 h	**4j**	60	
16	PhCO	rt	5 h	**4k**	50	

[a] Method A: cycloaddition reactions were performed after separation of hydroximoyl chlorides.
[b] Yields are based on aldoximes **1**.
[c] Method B: both nitrile oxide generation and cycloaddition reactions were performed without removal of BTMA ICl_2.
[d] BTMA ICl_4 was used in 1.4 equiv.
[e] BTMA ICl_4 was used in 1.2 equiv. in a short reaction time.

BTMA ICl_4 is not relatively effective in the reactions of aliphatic aldoximes. Probably some overreactions, for example α-chlorination, would occur to compensate the improvement of yields.[6]

It was found that the side product BTMA ICl_2 (**3**) was inert to both styrene and triethylamine so that **3** formed after the chlorination step would not always have to be removed from the reaction mixture. Skipping of this separation step must be a great advantage because we have to use quite a lot of diethyl ether for the completion of precipitation of undesired **3** (usually diethyl ether of five fold volumes to the dichloromethane is added), and because the resulting hydroximoyl chlorides are not always stable enough to be isolated. Thus, the one-flask procedure could be achieved as follows: Chlorination of oxime **1a**, as an example, with BTMA ICl_4 was performed in dichloromethane under the reaction conditions shown in Table 2. To the resulting pale yellow solution containing hydroximoyl chloride **2a** and BTMA ICl_2 were added styrene (1 equiv) and triethylamine (2 equiv). After the completion of cycloaddition reaction (checked by TLC), the reaction mixture was condensed in vacuo. Dilution of the residue with diethyl ether is a simple method of separation of cycloadduct **4a** from the insoluble BTMA ICl_2. Purification through a column chromatography gave **4a** in 62% yield. This one-flask procedure (Method B) could be successfully applied to aliphatic aldoximes also (entries 8, 10–12). The selective chlorination of the oxime moiety producing hydroximoyl chlorides should be emphasized since aliphatic aldoximes **1g** and **1i** have reactive substituents for homolytic chlorination reactions such as benzylic hydrogen and secondary alkyl group.

Another method (Method C) is also effective as an even simpler procedure in which all the reagents are put together in one flask from the first stage of reaction. Thus, to a solution of aldoxime **1a**, styrene (1 equiv), and triethylamine (2 equiv) in dichloromethane was added BTMA ICl_4 and the mixture was stirred at room temperature for a few hours. Through a work-up similar to that employed in Method B, the styrene cycloadduct **4a** was obtained in 70% yield. Now it is clear that BTMA ICl_4 can be effectively utilized for the in situ generation of nitrile oxides from aldoximes and that the resulting nitrile oxides can be trapped with the existing alkene dipolarophiles unless the alkenes are either highly reactive to BTMA ICl_4 or have substituent(s) susceptible to chlorination or oxidation by BTMA ICl_4.

It is well known[4c] that BTMA ICl_4 undergoes a variety of chlorination reactions such as electrophilic chlorination to electron rich aromatic and heteroaromatic rings, benzylic chlorination of aromatic compounds, chlorination of methyl ketones, and chlorine addition to unsaturated bonds. Ring chlorination of phenols is so rapid that this reaction is completed in dichloromethane in a short time at room temperature.[7] Other reactive aromatic compounds having electron donating substituents such as amino, acetamino, and alkoxyl moieties undergo smooth chlorination as well under similar conditions. The benzylic chlorination proceeds under reflux in tetrachloromethane in the presence of AIBN; the chlorinations of methyl ketones under reflux in methanol. It is surprising that the chlorine addition of styrene with BTMA ICl_4 is known to complete in 15 min at room temperature.[8] However, our styrene trapping experiment shown in Method C did not produce such an addition product, instead hydroximoyl chloride **2a** was the sole product. This indicates that the oxime chlorination of **1a** giving hydroximoyl chloride **2a** is much more rapid than the chlorine addition to styrene.

Table 3. Nitrile oxide generations and styrene cycloadditions by Method C (equimolar amounts of BTMA ICl_4 and aldoximes were used (the reaction conditions: in dichloromethane at room temperature for 6 h))

Entry	R of aldoxime **1**	Dipolarophile	Product	Yield[a] (%)
1	*p*-MeC_6H_4	Styrene	**4a**	70
2	*p*-$MeOC_6H_4$	Styrene	**4b**	45
3	*p*-$NO_2C_6H_4$	Styrene	**4c**	39
4	4-Py	Styrene	**4f**	28[b]
5	$PhCH_2$	Styrene	**4g**	35
6	*i*-Pr	Styrene	**4i**	42
7	*p*-MeC_6H_4	Ethyl acrylate	**4l**	50
8	*p*-MeC_6H_4	2-Propen-1-ol	**4m**	40

[a] Yields of isolated cycloadducts.
[b] The starting oxime **1f** was recovered in 25% yield.

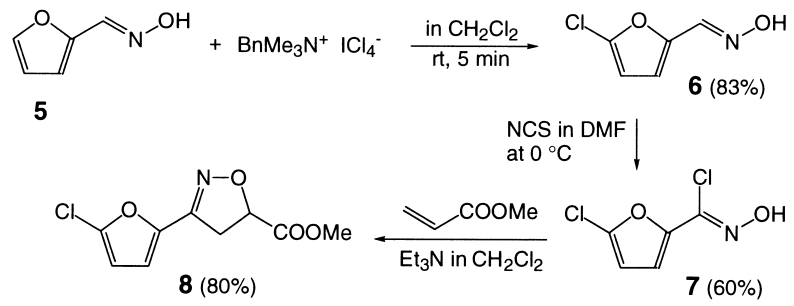
The relative reaction rates between the aldoxime chlorination and the chlorine addition to styrene would provide useful information for the establishment of reaction mechanism. Accordingly, we further examined some applications of the one-flask procedure (Method C) for a variety of combinations of aldoximes and alkene dipolarophiles, e.g. phenylacetaldehyde oxime (**1g**)/styrene, isobutyraldehyde oxime (**1i**)/styrene, *p*-methylbenzaldehyde oxime (**1a**)/ethyl acrylate, and **1a**/2-propen-1-ol (Table 3). Although the yields of cycloadducts are only fair, this one-pot procedure by Method C works effectively for a variety of combinations shown above.

Nucleophilic heterocycles such as furan and thiophene, especially when they are substituted by alkyl substituent(s) and therefore highly nucleophilic, are known to undergo ready ring chlorination with BTMA ICl_4.[9] Reaction of 2-furancarbaldehyde oxime (**5**) with BTMA ICl_4 under similar conditions did not produce the corresponding hydroximoyl chloride, but instead the selective ring chlorination took place to give 5-chloro-2-furancarbaldehyde oxime (**6**) as a single product in 83% yield (Scheme 2). A similar reaction with 2-thiophenecarbaldehyde oxime under comparable conditions led to the formation of a complex mixture of many products. Thiophene itself is chlorinated with BTMA ICl_4 producing tetrachlorothiophene and the formation of such polychlorinated products is a general pattern of reactivity of thiophene derivatives.[9] Although not isolated, the complex mixture formed above would contain some polychlorinated derivatives. On the contrary, the ring-chlorinated 2-furancarbaldehyde oxime **6** was rather sluggish both to further ring chlorination and oxime chlorination. Once one chloro substituent was introduced on the furan ring, the reactivity for chlorination leading to hydroximoyl chloride was extremely reduced. It took 7 h at room temperature to give hydroximoyl chloride **7** in 70% yield, still some starting material **6** remaining unreacted. However, the reaction of **5** with two equimolar amounts of BTMA ICl_4 gave only a trace amount of **7**. This reduced reactivity of **6** makes a striking contrast to the rapid reactions of electron-rich aromatic and aliphatic aldoximes.[10]

N-Chlorosuccinimide (NCS) is one of the reagents most widely used for the preparation of hydroximoyl chlorides from aldoximes, and usually *N*,*N*-dimethylformamide (DMF) is used as reaction solvent.[11] When the NCS method was applied to 2-furancarbaldehyde oxime (**5**) at 0°C in DMF, **6** was only obtained in 75% yield. On the other hand, **7** was produced in 60% yield in the reaction with two equimolar amounts of NCS. Thus, the NCS method is more suitable for the oxime chlorination of **6** than the BTMA ICl_4 method. The corresponding nitrile oxide which was generated upon treatment of **7** with triethylamine was trapped with methyl acrylate to give the cycloadduct **8** in 80% yield.

In the transformation of aldoximes to hydroximoyl chlorides with BTMA ICl_4, one molecule of hydrogen chloride is formed. When aldoximes have a basic site such as pyridinecarbaldehyde oximes **1d**–**f**, either of the starting oximes or the resulting hydroximoyl chlorides form hydrochloride salts. This makes either the chlorination reaction slower or the separation of hydroximoyl chlorides from BTMA ICl_2 difficult. Furthermore, protonic acid is known to facilitate the decomposition of hydroximoyl chlorides, especially this acid-catalyzed decomposition is crucial in the cases of rather unstable hydroximoyl chlorides derived from aliphatic aldoximes.[12] We therefore used MS 4A as a weak dehydrohalogenation reagent.

In the presence of MS 4A (500 mg for 1 mmol scale of reaction), the chlorination of aromatic aldoxime **1a**, followed by the nitrile oxide generation and the subsequent styrene cycloaddition, gave **4a** in an improved yield of 78%. Use of an increased amount of MS 4A did not increase the yield of **4a**. The reaction of 4-pyridinecarbaldehyde oxime **1f** in the presence of MS 4A enabled the isolation of free hydroximoyl chloride **2f**. Thus, after the completion of chlorination with BTMA ICl_4, diethyl ether was added to precipitate BTMA ICl_2. Evaporation of the ether filtrate gave 4-pyridinecarbohydroximoyl chloride (**2f**) in 85% yield. Although **2f** was hardly soluble in dichloromethane and chloroform, the styrene cycloadduct **4f** was obtained in 76% yield upon treatment with triethylamine and styrene. In



Scheme 2.

Table 4. Nitrile oxide generations and aldoximes and BTMA ICl_4 in the presence of MS 4A (Method A) (equimolar amounts of BTMA ICl_4 and aldoximes were used in the presence of MS 4A (500 mg for 1 mmol scale of reaction))

Entry	R	Conditions of chlorination			Yield of **4**
		Temp (°C)	Time	Product	
1	*p*-MeC_6H_4	rt	2 h	**4a**	78
2	*p*-$MeOC_6H_4$[a]	rt	2 h	**4a**	76
3	4-Py	rt	6 h	**4f**	76 (85)[b]
4	$PhCH_2$	rt	10 min	**4g**	66
5	$PhCH_2$	rt	0.5 h	**4g**	63
6	$PhCH_2$	rt	1 h	**4g**	61

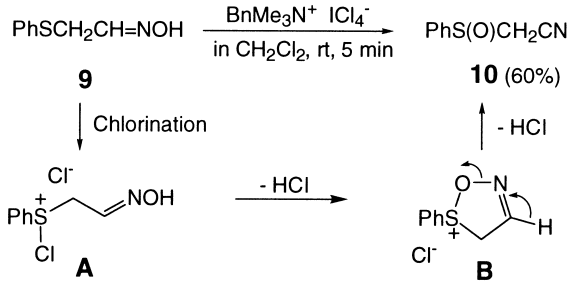
[a] MA 4A: 750 mg/1 mmol.
[b] Isolated yield of hydroximoyl chloride **2f** in parentheses.

chlorination of aliphatic aldoxime **1g** with BTMA ICl_4 it is rather difficult to optimize the reaction time since partial decomposition of the resulting **2g** takes place in a prolonged reaction time. We believe this decomposition is acid-catalyzed. In the presence of MS 4A, the yield of **4g** became almost independent upon the reaction time (Table 4).

Phenylthioacetaldehyde oxime (**9**) has an active methylene moiety so that it is possible that this position can be chlorinated in the reaction with BTMA ICl_4.[13] To our great surprise, the reaction of **9** with BTMA ICl_4 was so rapid that it was completed in a few minutes at room temperature. The single product obtained in 60% yield was phenylsulfinylacetonitrile (**10**) on the basis of spectral data and also by comparison with the authentic sample.[14] The presence of dipolarophiles (styrene or methyl acrylate) did not alter the reaction course, indicating that the corresponding hydroximoyl chloride was not involved in the reaction. A presumed reaction mechanism for the formation of **10** is illustrated in Scheme 3. Aldoxime **9** is rapidly chlorinated with BTMA ICl_4 at the sulfur atom **9** forming chlorosulfonium salt **A** which undergoes cyclization through an intramolecular nucleophilic substitution on the sulfur atom to give the oxathiazolium intermediate **B**. The nitrogen–oxygen bond cleavage of **B** must be very easy in a heterolytic manner since the resulting oxide anion can be highly stabilized by the positively charged sulfur atom leading to **10**.

In conclusion, the present BTMA ICl_4 oxime chlorination method has the following advantages:

1. BTMA ICl_4 is a stable solid and easy to handle. It can be weighed accurately so that the exact amount of chlorinating reagent needed for the reaction can be taken easily.



Scheme 3.

2. Although BTMA ICl_4 is hardly soluble in dichloromethane, the heterogeneous chlorination of oximes takes place rapidly. This is so especially for aldoximes having electron donating substituents on the oxime carbon.
3. With the progress of chlorination reaction, BTMA ICl_4 changes to BTMA ICl_2 which is then soluble in dichloromethane. Thus, disappearance of the suspension of BTMA ICl_4 indicates the point at which the reaction is almost completed.
4. The resulting BTMA ICl_2 is hardly soluble in diethyl ether so that separation of the hydroximoyl chloride from BTMA ICl_2 can be conveniently done simply by precipitation with the aid of diethyl ether and filtration.
5. Aromatic and heteroaromatic hydroximoyl chlorides can be prepared quantitatively and isolated by this method.
6. Aliphatic hydroximoyl chlorides, as well as aromatic and heteroaromatic ones, can be converted into the corresponding nitrile oxides and trapped with dipolarophiles in one flask.
7. In some cases, the in situ generation of nitrile oxides can be successfully done by starting from a mixture of aldoximes, dipolarophiles, triethylamine, and BTMA ICl_4.
8. MS 4A acts as a weak base to trap the hydrogen chloride formed in the reaction. Use of MS 4A enables the isolation of basic heterocyclic hydroximoyl chlorides and suppresses the acid-mediated decomposition of hydroximoyl chlorides.

Experimental

General procedure for the chlorination of aldoximes with BTMA ICl_4 (Method A)

Reaction of *p*-methylbenzaldehyde oxime (**1a**) is described as a typical example. To a solution of **1a** (135 mg, 1 mmol) in dichloromethane (5 ml, 0.2 M), was added BTMA ICl_4[15] (419 mg, 1 mmol). The greenish suspension disappeared in 10 min by vigorous stirring at room temperature to result in a yellow solution. After the stirring was continued for an additional 30 min, the mixture was diluted with diethyl ether (25 ml) and the resulting precipitate was filtered off. Evaporation of the filtrate in vacuo gave *p*-methylbenzohydroximoyl chloride (**2a**) as a pasty solid. This crude material was pure enough to be used in the next step.

To the above residue including hydroximoyl chloride **2a** were added dichloromethane (5 ml), styrene (105 mg, 1 mmol), and triethylamine (0.14 ml, 1 mmol) in this order. After stirring for 30 min at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane (15 ml×2). The combined extracts were dried over sodium sulfate and concentrated in vacuo to give a dark yellow residue, which was then purified through column chromatography on silica gel with hexane–diethyl ether (1:1 v/v) as an eluent to give the cycloadduct **4a** (147 mg, 63% based on **1a**) as a colorless solid.

General procedure for the chlorination of aldoximes with BTMA ICl_4 (Method B)

Reaction of *p*-methylbenzaldehyde oxime (**1a**) is described as a typical example. To a solution of **1a** (135 mg, 1 mmol) in dichloromethane (5 ml, 0.2 M), was added BTMA ICl_4 (419 mg, 1 mmol). A clear yellow solution was obtained by vigorous stirring at room temperature for 10 min. To the resulting solution were added styrene (105 mg, 1 mmol) and triethylamine (0.29 ml, 2 mmol) in this order. After stirring for 30 min at room temperature, the reaction mixture was condensed in vacuo and diluted with diethyl ether (25 ml). The precipitate of BTMA ICl_2 was filtered off. The filtrate was evaporated in vacuo to give the dark red residue which was chromatographed on silica gel with hexane–diethyl ether (1:1 v/v) to give **4a** (145 mg, 62% based on **1a**).

General procedure for the chlorination of aldoximes with BTMA ICl_4 (Method C)

Reaction of *p*-methylbenzaldehyde oxime (**1a**) is described as a typical example. To a solution of **1a** (135 mg, 1 mmol), styrene (105 mg, 1 mmol), and triethylamine (0.29 ml, 2 mmol) in dichloromethane (5 ml, 0.2 M), was added BTMA ICl_4 (419 mg, 1 mmol). The mixture was stirred at room temperature for 6 h and then diluted with ether (25 ml). The precipitate was filtered off, the filtrate was evaporated in vacuo, and then the dark red residue was chromatographed on silica gel with hexane–diethyl ether (1:1 v/v) to give **4a** (163 mg, 70% based on **1a**).

In some cases, hydroximoyl chlorides **2** were isolated and characterized by ^{1}H NMR (400 MHz).

***p*-Methylbenzohydroximoyl chloride (2a).** Light yellow solid; ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s, Me), 7.20 (2H, dd, J=8.5 and 1.7 Hz, Tolyl), 7.71 (2H, dd, J=8.5 and 1.7 Hz, Tolyl), and 8.62 (1H, br. s, NOH).

***p*-Methoxybenzohydroximoyl chloride (2b).** Light yellow solid; ^{1}H NMR ($CDCl_3$) δ 3.84 (3H, s, MeO), 6.91 (2H, dd, J=8.5 and 2.2 Hz, Ar), 7.77 (2H, dd, J=8.5 and 2.2 Hz, Ar), and 8.47 (1H, br. s, NOH).

***p*-Nitrobenzohydroximoyl chloride (2c).** Light yellow solid; ^{1}H NMR ($CDCl_3$) δ 8.05 (2H, dd, J=9.0 and 2.2 Hz, Ar), and 8.27 (2H, dd, J=9.0 and 2.2 Hz, Ar), and 8.91 (1H, br. s, NOH).

4-Pyridinecarbohydroximoyl chloride (2f). Light yellow solid; ^{1}H NMR ($CDCl_3$) δ 7.77 (2H, dd, J=4.6 and 1.6 Hz, Ar), 8.60 (1H, br. s, NOH), and 8.70 (2H, dd, J=4.6 and 1.6 Hz, Ar).

Spectral data of the cycloadducts **4** are given below (^{1}H and ^{13}C NMR, 400 MHz):

3-(*p*-Methylphenyl)-5-phenyl-2-isoxazoline (4a). Colorless scales from CH_2Cl_2–hexane; mp 100–101°C; ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s, Me), 3.32 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.2 Hz, one of H-4), 3.76 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=10.9 Hz, the other of H-4), 5.71 (1H, dd, J_{5-4}=10.9 and 8.2 Hz, H-5), 7.21 (2H, dd, J=8.5 and 1.7 Hz, Tolyl), 7.29–7.41 (5H, m, Ph), and 7.58 (2H, dd, J=8.5 and 1.7 Hz, Toyl); ^{13}C NMR ($CDCl_3$) δ 21.42 (Me), 43.29 (C-4), 82.39 (C-5), 125.87, 126.65, 126.68, 128.16, 128.72, 129.42, 140.37, 141.04 (Ph and Ar), and 156.04 (C-3), MS *m*/*z* (rel. intensity, %) 237 (M^+, base peak), 133 (20), 104 (84), 91 (23), 77 (13). Anal. Found: C, 80.98; H, 6.43; N, 5.86. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90.

3-(*p*-Methoxyphenyl)-5-phenyl-2-isoxazoline (4b). Colorless plates from CH_2Cl_2–hexane; mp 104–105°C; ^{1}H NMR ($CDCl_3$) δ 3.32 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.2 Hz, one of H-4), 3.76 (1 H, dd, J_{gem}=16.7 Hz and J_{4-5}=10.9 Hz, the other of H-4), 3.84 (3H, s, MeO), 5.71 (1H, dd, J_{5-4}=10.9 and 8.2 Hz, H-5), 6.93 (2H, dd, J=8.9 and 1.2 Hz, Ar), 7.29–7.41 (5H, m, Ph), and 7.63 (2H, dd, J=8.9 and 1.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 43.44 (C-4), 55.35 (MeO), 82.29 (C-5), 114.14, 122.04, 125.87, 128.14, 128.27, 128.72, 141.09 (Ph and Ar), 155.66 (C-3), and 161.09 (Ar); MS *m*/*z* (rel. intensity, %) 254 (M^++1, base peak), 253 (73, M^+), 221 (13), 207 (12), 154 (17), 147 (40), 136 (20), and 73 (24). Anal. Found: C, 75.78; H, 6.03; N, 5.46. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.96; N, 5.53.

3-(*p*-Nitrophenyl)-5-phenyl-2-isoxazoline (4c). Yellow prisms from CH_2Cl_2–hexane; mp 127–129°C; ^{1}H NMR ($CDCl_3$) δ 3.35 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.4 Hz, one of H-4), 3.81 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=11.1 Hz, the other of H-4), 5.83 (1H, dd, J_{5-4}=11.1 and 8.4 Hz, H-5), 7.33–7.43 (5H, m, Ph), 7.86 (2H, ddd, J=9.1, 2.2, and 2.2 Hz, Ar), and 8.27 (2H, ddd, J=9.1, 2.2, and 2.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 42.47 (C-4), 83.64 (C-5), 124.02, 125.81, 127.41, 128.56, 128.91, 135.56, 140.12 (Ph and Ar), and 154.60 (C-3); MS *m*/*z* (rel. intensity, %) 268 (M^+, 92), 192 (30), 162 (37), 104 (base peak). Anal. Found: C, 67.05; H, 4.58; N, 10.43. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44.

5-Phenyl-3-(2-pyridyl)-2-isoxazoline (4d). Colorless plates from CH_2Cl_2–hexane; mp 64–66°C; IR (KBr) 3040, 2920, 1580, 1440, 1360, 900, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (1H, dd, J_{gem}=17.4 Hz and J_{4-5}=8.5 Hz, one of H-4), 3.93 (1H, dd, J_{gem}=17.4 Hz and J_{4-5}=11.1 Hz, the other of H-4), 5.79 (1H, dd, J_{5-4}=11.1 and 8.5 Hz, H-5), 7.26–7.42 (6H, m, Ar), 7.73 (1H, ddd, J=8.0, 1.8, and 0.6 Hz, Ar), 8.07 (1H, d, J=8.0 Hz, Ar), and 8.60 (1H, dd, J=5.0 and 0.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 42.52 (C-4), 83.28 (C-5), 121.80, 124.23, 125.90, 128.21, 128.72, 136.37, 140.74, and 149.33 (Ph, Ar, and C-3); MS *m*/*z* (rel. intensity, %) 224 (M^+, base peak), 207 (25), 193 (36), 147 (43), 104 (27), and 78 (26). Anal. Found: C, 75.00; H, 5.39; N, 12.42. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49.

5-Phenyl-3-(3-pyridyl)-2-isoxazoline (4e). Colorless plates from CH_2Cl_2–hexane; mp 69–71°C; IR (KBr) 3010, 1590, 1430, 1350, 1010, 910, 760, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.2 Hz, one of H-4), 3.80 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.2 Hz, one of H-4), 3.80 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=10.9 Hz, the other of H-4), 5.79 (1H, dd, J_{5-4}=10.9 and 8.2 Hz, H-5), 7.31–7.40 (6H, m, Ar), 8.09 (1H, ddd, J=8.0, 1.9, and

1.9 Hz, Ar), 8.65 (1H, dd, J=4.8 and 1.7 Hz, Ar), and 8.80 (1H, d, J=2.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 42.53 (C-4), 82.94 (C-5), 123.63, 125.71, 125.82, 128.43, 128.85, 133.71, 140.41, 147.84, 151.09 (Ph and Ar) and 153.77 (C-3); MS *m*/*z* (rel. intensity, %) 224 (M^+, 67), 153 (80), 136 (52), 107 (72), 89 (69), and 77 (base peak). Anal. Found: C, 75.05; H, 5.42; N, 12.44. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49.

5-Phenyl-3-(4-pyridyl)-2-isoxazoline (4f). Colorless plates from CH_2Cl_2–hexane; mp 67–69°C; IR (KBr) 3000, 2200, 1590, 1400, 1350, 900, 810, 720, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.32 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.5 Hz, one of H-4), 3.76 (1H, dd, J_{gem}=16.7 Hz and J_{4-5} =11.1 Hz, the other of H-4), 5.81 (1H, dd, J_{5-4}=11.1 and 8.5 Hz, H-5), 7.32–7.42 (5H, m, Ph), 7.54 (2H, dd, J=4.5 and 1.7 Hz, Ar), and 8.68 (2H, dd, J=4.5 and 1.7 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 42.11 (C-4), 83.46 (C-5), 120.88, 125.81, 128.52, 128.88, 136.77, 140.19, 150.46 (Ph and Ar), and 154.59 (C-3); MS *m*/*z* (rel. intensity, %) 224 (M^+, 58) and 104 (base peak). Anal. Found: C, 74.98; H, 5.42; N, 12.44. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49.

3-Benzyl-5-phenyl-2-isoxazoline (4g). Colorless oil; IR (neat) 3040, 2920, 1610, 1500, 1460, 1430, 1080, 1040, 760, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.75 (1H, dd, J_{gem}=17.1 Hz and J_{4-5}=8.4 Hz, one of H-4), 3.18 (1H, dd, J_{gem}=17.1 Hz and J_{4-5}=10.9 Hz, the other of H-4), 3.64 (1H, d, J_{gem}=14.8 Hz, one of $PhCH_2$), 3.71 (1H, d, J_{gem}=14.8 Hz, the other of $PhCH_2$), 5.47 (1H, dd, J_{5-4} =8.4 and 10.9 Hz, H-5), and 7.20–7.30 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 33.91 ($PhCH_2$), 44.27 (C-4), 81.61 (C-5), 125.56, 126.92, 127.82, 128.44, 128.64, 135.47, 140.84 (each Ph), and 157.23 (C-3); MS *m*/*z* (rel. intensity, %) 238 (M^++1, base peak), 107 (6), 91 (16), and 77 (4). Anal. Found: C, 80.67; H, 6.41; N, 5.85. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90.

5-Phenyl-3-propyl-2-isoxazoline (4h). Light yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J=7.5 Hz, CH_3 of *n*-Pr), 1.62 (2H, tt, J=7.5 and 7.5 Hz, CH_2 of *n*-Pr), 2.36 (2H, t, J=7.5 Hz, CH_2 of *n*-Pr), 2.89 (1H, dd, J_{gem}=16.9 Hz and J_{4-5}=8.2 Hz, one of H-4), 3.35 (1H, dd, J_{gem}=16.9 Hz and J_{4-5}=10.9 Hz, the other of H-4), 5.54 (1H, dd, J_{5-4}=10.9 and 8.2 Hz, H-5), 7.29–7.38 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 13.71, 19.76, 29.57 (each *n*-Pr), 45.30 (C-4), 81.16 (C-5), 125.67, 127.94, 128.63, 141.37 (each Ph), and 158.34 (C-3); MS *m*/*z* (rel. intensity, %) 189 (M^+, 55), 161 (21), 117 (18), 104 (base peak), 91 (17), and 77 (20). Anal. Found: C, 75.89; H, 8.00; N, 7.39. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40.

5-Phenyl-3-isopropyl-2-isoxazoline (4i). Light yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, d, J=7.0 Hz, one of Me), 1.19 (3H, d, J=7.0 Hz, the other of Me), 2.75 (1H, sep, J=7.0 Hz, Me_2CH), 2.94 (1H, dd, J_{gem}=16.9 Hz and J_{4-5} =8.2 Hz, one of H-4), 3.63 (1H, dd, J_{gem}=16.9 Hz and J_{4-5} =10.9 Hz, the other of H-4), 5.53 (1H, dd, J_{5-4}=10.9 and 8.2 Hz, H-5), and 7.27–7.38 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 20.08, 20.09, 27.89 (each *i*-Pr), 43.24 (C-4), 81.24 (C-5), 125.67, 127.93, 128.62, 141.39 (each Ph), and 162.98 (C-3); MS *m*/*z* (rel. intensity, %) 189 (M^+, 58), 117 (18), 104 (base peak), and 77 (21). Anal. Found: C, 75.91; H, 7.98; N, 7.45. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N. 7.40.

3-(*t*-Butyl)-5-phenyl-2-isoxazoline (4j). Light yellow oil; IR (neat) 2990, 1610, 1360, 1250, 890, 760, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (9H, s, *t*-Bu), 2.92 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=8.1 Hz, one of H-4), 3.39 (1H, dd, J_{gem}=16.7 Hz and J_{4-5}=10.6 Hz, the other of H-4), 5.52 (1H, dd, J_{5-4}=8.1 and 10.6 Hz, H-5), and 7.25–7.37 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 28.05, 32.97 (each *t*-Bu), 42.59 (C-4), 81.61 (C-5), 125.62, 127.87, 128.57, 141.40 (each Ph), and 165.39 (C-3); MS *m*/*z* (rel. intensity, %) 203 (M^+, 94), 188 (21), 170 (11), 131 (24), 104 (base peak), 97 (52), and 77 (23). Anal. Found: C, 76.45; H, 8.44; N, 6.81. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89.

3-Benzoyl-5-phenyl-2-isoxazoline (4k). Light yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.39 (1H, dd, J_{gem}=17.6 Hz and J_{4-5} =8.7 Hz, one of H-4), 3.78 (1H, dd, J_{gem}=17.6 Hz and J_{4-5} =11.4 Hz, the other of H-4), 5.77 (1H, dd, J_{5-4}=8.7 and 11.4 Hz, H-5), 7.33–7.42 (5H, m, Ph), 7.48 (2H, m, Ar), 7.61 (1H, m, Ar), and 8.24 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 41.82 (C-4), 84.21 (C-5), 125.90, 128.40, 128.61, 128.87, 130.33, 133.63, 135.75, 139.66 (each Ph), 157.37 (C-3), and 186.20 (CO); MS *m*/*z* (rel. intensity, %) 252 (M^++1, 65) and 105 (base peak). Anal. Found: C, 76.25; H, 5.28; N, 5.73. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57.

Reaction of 2-furancarbaldehyde oxime (6) with BTMA ICl_4

To a stirred solution of 2-furancarbaldehyde oxime (**5**, 111 mg, 1 mmol) in dichloromethane (5 ml, 0.2 M), was added BTMA ICl_4 (419 mg, 1 mmol). After stirring for 5 min at room temperature, the reaction mixture was diluted with diethyl ether (25 ml) and the precipitate was filtered off. The filtrate was evaporated in vacuo, and then the dark red residue was chromatographed on silica gel with hexane–diethyl ether (1:1 v/v) to give 5-chloro-2-furancarbaldehyde oxime (**6**, 121 mg, 83%) as a colorless solid. The chlorination and cycloaddition with methyl acrylate were performed according to Method A to give 5-chloro-2-furancarbohydroximoyl chloride (**7**) in 60% yield and methyl 3-(5-chloro-2-furyl)-2-isoxazoline-5-carboxylate (**8**) in 80% yield.

5-Chloro-2-furancarbaldehyde oxime (6). Colorless plates from Et_2O–hexane; mp 110–111°C; IR (KBr) 3200, 1630, 1590, 1200, 1010, 970, 930, 840, and 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, d, J=3.5 Hz, Furyl), 7.29 (1H, d, J=3.5 Hz, Furyl), 7.42 (1H, s, CH=N), and 8.80 (1H, br. s, NOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 109.11, 120.36, 136.28, 138.40 (each Ar), and 144.72 (CH=NOH); MS *m*/*z* (rel. intensity, %) 137 (11), 121 (7), 81 (31), and 69 (base peak). Anal. Found: C, 42.29; H, 3.06; N, 9.87. Calcd for $C_5H_4NO_2Cl$: C, 41.26; H, 2.77; N, 9.62.

5-Chloro-2-furancarbohydroximoyl chloride (7). Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (1H, d, J=3.4 Hz, Furyl), and 6.85 (1H, d, J=3.4 Hz, Furyl), and 8.98 (1H, br. s, NOH).

Methyl 3-(5-chloro-2-furyl)-2-isoxazoline-5-carboxylate (8). Colorless plates from CH_2Cl_2–hexane; mp 101–102°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (1H, dd, J_{gem}=16.9 Hz and J_{4-5}=11.1 Hz, one of H-4), 3.62 (1H, dd, J_{gem}=16.9 Hz and J_{4-5}=7.0 Hz, the other of H-4), 3.82 (3H, s, COOMe), 5.16 (1H, dd, J_{5-4}=7.0 and 11.1 Hz, H-5), 6.29 (1H, d, J=3.6 Hz, Furyl), and 6.77 (1H, d, J=3.6 Hz, Furyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ 38.41 (C-4), 52.91 (COOMe), 77.75 (C-5), 108.71, 114.29, 139.37, 143.37 (each Ar), 147.56 (C-3), and 170.17 (COOMe); MS *m*/*z* (rel. intensity, %) 229 (M^+, base peak), 170 (96), 142 (25), 114 (39), 101 (18), and 73 (31). Anal. Found: C, 47.16; H, 3.49; N, 6.15. Calcd for $C_9H_8NO_4Cl$: C, 47.08; H, 3.51; N, 6.10.

Reaction of phenylthioacetaldehyde oxime (9) with BTMA ICl_4

To a stirred suspension of MS 4A (500 mg) and phenylthioacetaldoxime (167 mg, 1 mmol) in dichloromethane (5 ml, 0.2 M), was added BTMA ICl_4 (419 mg, 1 mmol) and stirred vigorously. After stirring for 5 min at room temperature, the reaction mixture was diluted with diethyl ether (25 ml) and the precipitate was filtered off. The filtrate was evaporated in vacuo and the dark red residue was chromatographed on silica gel with hexane–diethyl ether (1:1 v/v) to give phenylsulfinylacetonitrile (**10**, 99 mg, 60%) as a colorless solid. **10**: Colorless prisms from diethyl ether–hexane; mp 64–65°C; IR (neat) 3020, 2358, 2341, 1215, 758, and 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68, 3.84 (each 1H, d, J_{gem}=15.7 Hz, CH_2), 7.59–7.63 (3H, m, Ph), and 7.73–7.81 (2H, m, Ph); ^{13}C NMR (400 MHz, $CDCl_3$) δ 44.67 (CH_2), 110.95 (CN), 124.12, 129.73, 132.79, and 141.41 (each Ph); MS *m*/*z* (rel. intensity, %) 165 (M^+, 7), 149 (11), 125 (base peak), 109 (10.1), 97 (29), and 77 (30). Anal. Found: C, 58.28; H, 4.30; N, 8.55. Calcd for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48.

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5. *E*-**1a**: mp 108–110°C; *Z*-**1a**: mp 79–80°C. Pure *E*-**1a** is obtained after crystallization, but it gradually isomerizes at room temperature to *Z*-**1a** resulting in an *E*/*Z*-mixture.

6. Although not isolated, the crude reaction mixture from **1g** includes lachrymatory compound(s).

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15. BTMA ICl_4 can be prepared as follows: to a stirred solution of iodine trichloride (ICl_3, 25 g, 0.154 mol) in CH_2Cl_2 (600 ml) was added benzyltrimethylammonium chloride (BTMA Cl, 28.6 g, 0.154 mol). The mixture was stirred at room temperature for 1 h to give the yellow precipitate of BTMA ICl_4 which was then washed with CH_2Cl_2 (53.5 g, quant).[4]