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Improved Procedure for the Synthesis of Enamine *N*-Oxides

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Received February 4, 2008

An improved procedure for the preparation of enamine *N*-oxides involving aminolysis of epoxides, chlorination, *N*-oxidation, and dehydrochlorination is described. Although isolated β-chloroamine *N*-oxides are prone to rearrangements when isolated, these side reactions can be slowed by the presence of stabilizing organic acids. The scope and limitations of this strategy are discussed.

Tertiary amine *N*-oxides [R_3NO] are commonly encountered in organic chemistry,[1] being used in transition-metal-catalyzed oxidations[2] as protecting groups for sensitive tertiary amines[3] and in some cases as chiral promoters for transition-metal-catalyzed reactions[4] or in organocatalysts.[5] However, enamine *N*-oxides **1**, i.e., tertiary amine *N*-oxides where the nitrogen bears vinylic (but not aromatic or heteroaromatic) substituents, have only been the object of scarce reports (Figure 1).[6–8]

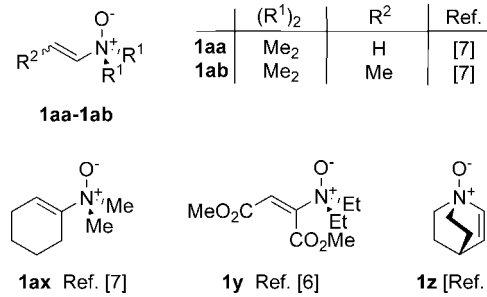

FIGURE 1. All known enamine *N*-oxides reported in the literature (1900−2008) prior to these studies.[9]

Direct *N*-oxidation of enamines is not a viable strategy to such compounds. Such attempted oxidations usually lead instead to complex reaction mixtures, comprising of mainly amides, α-amino ketones, and in some cases, unstable amino epoxides. All of these products are consistent with a *C*- rather than *N*-oxidation pathway.[10] Only two successful approaches to the synthesis of genuine enamine *N*-oxides have been reported: retro-Cope addition of a *N*,*N*-dialkylhydroxylamine to activated alkynes[6] and HX elimination of tertiary amine *N*-oxides substituted by a suitable β-leaving group.[7,8] However, the species of the retro-Cope addition have limited stability, often undergoing subsequent rearrangements.[11] The HX elimination strategy, which we refer to as the "Richmond-O'Neil" procedure, requires (a) preparation of tertiary amines bearing leaving groups on the β-position, (b) oxidation to the *N*-oxide, and finally (c) deprotonation at the α-position to the *N*-oxide to induce the desired C=C double-bond formation. However, use of this "Richmond-O'Neil" strategy is complicated by the poor literature availability and limited stability of many potential β-leaving group amine precursors and in some cases the need for aqueous workup and tedious drying of water-soluble organic salts.[7]

In connection with another project, we had need of a range of enamine *N*-oxides. Here we present a useful form of the

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(1) For reviews on the synthesis and reactivity of tertiary amines *N*-oxides, see inter alia: Albini, A. *Synthesis* **1993**, 263–277.

(2) In Upjohn dihydroxylation, see, for instance: VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. Choudary, B. M.; Chodari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 5341–5349. Ley, S. V.; Ramarao, C.; Lee, A.-L.; Ostergaard, N.; Smith, S. C.; Shirley, I. M. *Org. Lett.* **2003**, *5*, 185–187. Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78. In Sharpless asymmetric dihydroxylation: Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965–3968. Branco, L. C.; Afonso, C. A. M. *J. Org. Chem.* **2004**, *69*, 4381–4389. In perruthenate-catalyzed oxidation of alcohols to carboxylic acids: Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316. In Kornblum-like oxidation of benzylic halides to aromatic aldehydes: Barbry, D.; Champagne, P. *Tetrahedron Lett.* **1996**, *37*, 7725–7726.

(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed; John Wiley & Sons; New York, 1999.

(4) (a) Chen, F.-X.; Zhou, H.; Liu, X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Chem. Eur. J.* **2004**, *10*, 4790–4797. (b) Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Synlett* **1995**, 1085–1086. Derdau, V.; Laschat, S.; Jones, P. G. *Heterocycles* **1998**, *48*, 1445–1453.

(5) Chen, F.-X.; Qin, B.; Feng, X.; Zhangb, G.; Jiang, Y. *Tetrahedron* **2004**, *60*, 10449–10460. Huang, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X. *J. Org. Chem.* **2007**, *72*, 204–208. Qin, B.; Liu, X.; Shi, J.; Zheng, K.; Zhao, H.; Feng, X. *J. Org. Chem.* **2007**, *72*, 2374–2378.

(6) (a) Winterfelt, E.; Krohn, W. *Chem.Ber.* **1969**, *102*, 2336–2345. (b) Hwu, J. R.; Patel, H. V.; Lin, R. J.; Gray, M. O. *J. Org. Chem.* **1994**, *59*, 15771582.

(7) Krouwer, J. S.; Richmond, J. P. *J. Org. Chem.* **1978**, *43*, 2464–2466.

(8) O'Neil, I. A.; Wynn, D.; Lai, J. Y. Q. *Tet. Lett.* **2000**, *41*, 271–274.

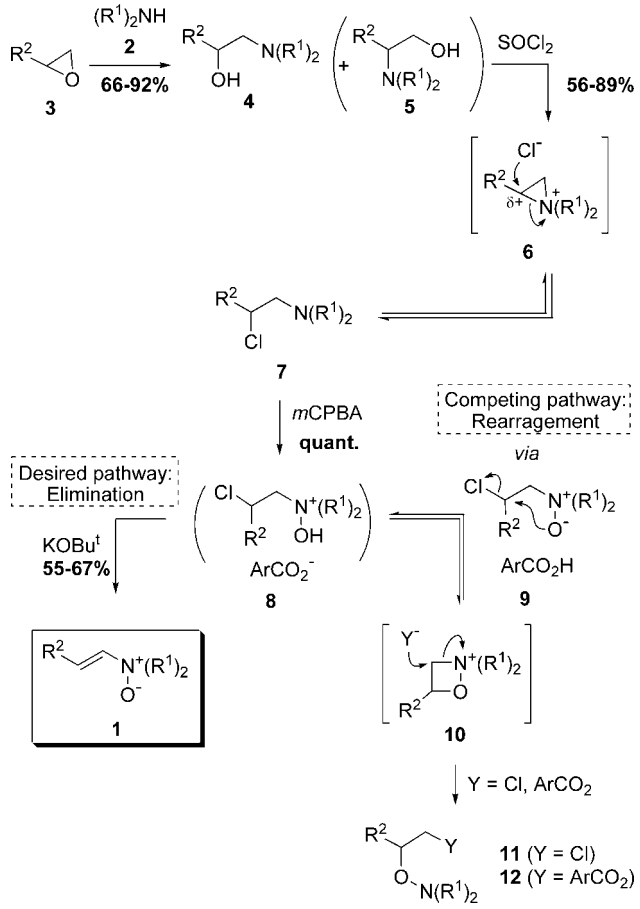
(9) Searches using Beilstein and SciFinder databases, March 2008.

(10) Oxidation of enamines: (a) H_2O_2 oxidation yielding an aminoepoxide: Coffen, D. L.; Korzan, D. G. *J. Org. Chem.* **1971**, *36*, 390–395. (b) *m*-CPBA oxidation yielding β-hydroxy amines (via epoxidation, epoxide opening and nucleophilic attack of the resulting iminium): Sunose, M.; Anderson, K. M.; Orpen, A. G.; Gallagher, T.; Macdonald, S. J. F. *Tetrahedron Lett.* **1998**, *39*, 8885–8888. (c) *m*-CPBA oxidation yielding an amino epoxide: Iwasa, K.; Sugiura, M.; Takao, N. *J. Org. Chem.* **1982**, 4275–4280. (d) O_2 oxidation yielding α-amino ketones and products of the oxidative cleavage of the C=C double bond: Jerussi, R. A. *J. Org. Chem.* **1969**, *34*, 3648–3650. (e) Blau, K.; Voerckel, V. *J.Prakt. Chem.* **1989**, *331*, 285–292. (f) Blau, K.; Kapst, U.; Voerckel, V. *J. Prakt. Chem.* **1989**, *331*, 671–676. (g) Dimethyldioxirane oxidation yielding an unstable α-amino epoxide: Adam, W.; Ahrweiler, M.; Paulini, K.; Reiβig, H.-U.; Voerckel, V. *Chem.Ber.* **1992**, *125*, 2719–2721. (h) The related reaction of enamines with elemental sulphur yields thioamides: Murata, S.; Suzuki, K.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 361–365, and is considered to be a key step of the Willgerodt−Kindler reaction.

(11) Addition of Et_2N-OH to methyl propiolate (1 equiv) in Et_2O at 0°C provides a white insoluble solid, presumably the expected *N*-oxide. However, as described by Winterfelt and Krohn for a similar addition,[6a] this product rearranges within minutes in $CDCl_3$ at rt into a less polar one; NMR of the rearranged product [olefinic signals: ^1H δ = 7.48 (d, J = 12.5 Hz) and 5.47 (d, J = 12.5 Hz); ^{13}C δ = 164.9, 85.4] closely matches that reported by Hwu *et al.*[6b] as the product of a similar addition. However, we believe these signals should be assigned to the rearranged product $Et_2N-O-CH=CH-CO_2Me$. See also: Bottle, S.; Busfield, W. K.; Jenkins, I. D.; Skelton, B. W.; White, A. H.; Rizzardo, E.; Solomon, D. H. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1001–1008.

10.1021/jo8002166 CCC: $40.75
Published on Web 05/07/2008

SCHEME 1. New Epoxide-Based Route to Enamine *N*-Oxides 1



"Richmond-O'Neil" procedure (Scheme 1) and comment on the pitfalls that can befall the syntheses of these interesting polar compounds.

Several simple (2-chloroethyl)amines **7** (R^2 = H) are commercial as hydrochloride salts, and the corresponding free amines[12] can be used as an entry point into this procedure.[13] In the case of substituted β-chloroamines **7** (R^2 = *n*-Bu, *c*-C_6H_{11}, and $PhCH_2CH_2$), our preparation is based on a sequence of epoxide aminolysis and chlorination of the resulting amino alcohols. The opening of terminal epoxides **1**[14] with secondary amines **2** is known to proceed, in general, from the least hindered side to provide regioisomer **4** (or mixtures with the regioisomer **5**).[15] Direct treatment of these products with $SOCl_2$ leads to single β-chloro substituted amines **7** via regiospecific opening of the aziridinium ions **6**, presumably via the formation of a close-contact ion pair.[16] Dropwise addition of **7** to a solution of *m*-chloroperbenzoic acid[17] (*m*-CPBA) in $CHCl_3$ or CH_2Cl_2 leads to the easily isolated salts **8**[18] (Supporting Information).

Attempted purification of **8** is fraught with difficulties as it often unmasks the reactive free *N*-oxides **9**. The free oxides ($pK_a \sim 4.56-4.75$)[19] have appreciable *O*-nucleophilicity. In a remarkable study, Owari and co-workers showed that *N*-oxides of nitrogen mustards undergo intramolecular nucleophilic displacement of a chloride by the oxygen of the *N*-oxide, rearranging to form a highly reactive oxazetidinium.[20] Transposed to our case, a similar pathway leads to oxazetidinium **10**; subsequent opening by either chloride or chlorobenzoate anions leads to the rearrangement products **11** and **12**, respectively, which we could isolate in several instances. Such rearrangement processes had previously been noted only in passing as an artifact in attempted *N*-oxidations of nitrogen mustards[21] and in the synthesis of the anticancer agent "chlorambucil".[22] Consistent with this picture, attempted oxidation of **7ea** (R^1 = Bu^i, R^2 = H) fashioned only a mixture of the desired salt **8** and the corresponding rearranged product **12ea**. We ascribe this behavior to Thorpe−Ingold effect[23] promoted closure to **10**. For this reason, the majority of our studies have concentrated on methyl and pyrrolidino substitutents in the R^1 position. Similarly, no attempt was made to prepare **7ef** (R^2 = Ph) as it is highly likely that the enhanced benzylic nature of the leaving group in **8** will favor decomposition via **10**. Deprotonation is also an issue with enamine *N*-oxide **1de**. The activated allylic/benzylic position in **1de** apparently suffers from competing proton abstraction leading to a complex mixture. Attempted synthesis of **1ga** equally failed, as none of the expected *N*-oxide **8ga** could be isolated from the complex[24] (black) mixture of products obtained after the oxidation of the corresponding β-chloro(diphenyl)amine **7ga** (this behavior was attributed to competitive oxidation at the aromatic ring).[25] We could also show that mildly basic conditions (3 equiv of K_2CO_3, CH_3CN) induced selective "Owari-type" rearrangement of the

(12) Hickmott, P. W.; Wood, S.; Murray-Rust, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2033–2038, Unhindered β-chloroamines should be prepared no more than 24 h before use, as they exhibit a propensity to spontaneous ring closure to the corresponding aziridinium salts.

(13) Some 2-chloroethylamines were prepared—when the corresponding hydrochlorides were not commercially available—by reacting α-chloroacetyl chloride with a dialkylamine in the presence of Et_3N to yield the corresponding α-chloroamide, followed by reduction with $BH_3 \cdot Me_2S$ to the β-chloroamine (Supporting Information). This alternative avoids the use of toxic oxirane.

(14) Non-commercial epoxides were prepared in 74−85% yield by *m*-CPBA epoxidation of the corresponding terminal alkenes.

(15) Fujiwara, M.; Imada, M.; Babaand, A.; Matsuda, H. *Tetrahedron Lett.* **1989**, *30*, 739–742, If R^2 = alkyl, only **4** is obtained. However, if R^2 is an aryl on an electron-withdrawing group such as CO_2R, mixtures contaminated with the minor regioisomer **5** are obtained. The introduction of such groups would however be detrimental in our synthesis, since in the later steps it would favor rearrangement via the 1,2-oxazetidinium intermediate **10**.

(16) See, for instance: D'hooghe, M.; Speybroeck, V. V.; Waroquier, M.; Kimpe, N. D. *Chem. Commun.* **2006**, 1554–1556.

(17) This order of addition is essential: we assume that protonation of the *N*-oxides prevents the formation of the 1,2-oxazetidinium **10** and therefore limits the formation of "Owari" rearrangement products.

(18) The salts **8** are very hygroscopic, and their stability varies with their degree of substitution: when R^2 = H, slow but steady degradation takes place at rt and can be monitored by ^1H NMR. These samples should be stored at 0−4 °C and used within 1 week. When R^2 = alkyl (**8db**, **8dc**, **8dd**), no significant change in the ^1H NMR spectra was noted upon storage in a closed flask at room temperature for 2 weeks.

(19) pK_a of queous solutions of Me_3NO: Perrin, D. D., *Dissociation constants of organic bases in aqueous solutions*; Butterworths: London, 1965; p 473. Lin, T.-Y.; Timasheff, S. N. *Biochemistry* **1994**, *33*, 12695–12701. Qu, Y.; Bolen, D. W. *Biochemistry* **2003**, *42*, 5837–5849. In organic media, see: Chmurzýnski, L.; Pawlak, Z. *J. Chem. Thermodynam.* **1998**, *30*, 27–35.

(20) Owari, S. *Chem. Pharm. Bull.* **1953**, *1*, 353–357.

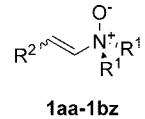
(21) Sakurai, Y.; Izumi, M. *Chem. Pharm. Bull.* **1953**, *1*, 297–301. Kuwada, Y. *Chem. Pharm. Bull.* **1960**, *8*, 807–814.

(22) Tercel, M.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1995**, *38*, 1247–1252.

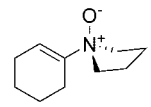
(23) (a) Thorpe−Ingold effect: Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305–329. Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *121*, 1117–1198. (b) Extended concept usually referred to as a *gem*-dimethyl or *gem*-dialkyl effect: Hammond G. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; pp 462−470; Smith, S. W.; Newman, M. S. *J. Am. Chem. Soc.* **1968**, *88*, 1253–1957.

(24) Similar observations were reported by Sakurai and Izumi during the oxidation of *N*-aryl nitrogen mustards with peracetic acid (ref. 21).

(25) For examples of *ortho*-oxidations during oxidative degradation of *N,N*-disubstituted anilines (Boyland−Sims oxidation), as well as during side reactions of the corresponding *N*-oxides, see: Boyland, E.; Manson, D.; Sims, P. J. *J. Chem. Soc.* **1953**, 3623–3626. Huisgen, R. *Chem. Ber.* **1959**, *92*, 3223–3236. Srinivasan, C.; Perumal, S.; Arumugam, N. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1855–1858. Behrman, E. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, *3*, 305–306.



1aa-1bz



1dx
(55% from *cis*-**7dx**)

	$(R^1)_2$	R^2	Yield (%) from **7**	
1aa	Me_2	H	60	
1ca	$(CH_2)_5$	H	62	
1da	$(CH_2)_4$	H	60	
1db	$(CH_2)_4$	n-C_4H_9	58	
1dc	$(CH_2)_4$	c-C_6H_{11}	56	
1dd	$(CH_2)_4$	$Ph(CH_2)_2$	67	
1de	$(CH_2)_4$	$PhCH_2$		unsuccessful
1ea	(i-Bu)$_2$	H		unsuccessful
1fa	Bn_2	H		unsuccessful
1ga	Ph_2	H		unsuccessful
1ef	(i-Bu)$_2$	Ph		unsuccessful

FIGURE 2. Enamine *N*-oxides prepared (**1aa**, **1ca**, **1da**−**dd**, and **1dx**) or unsuccessfully targeted (**1de**, **1ea**−**ga**, and **1ef**) during this work.

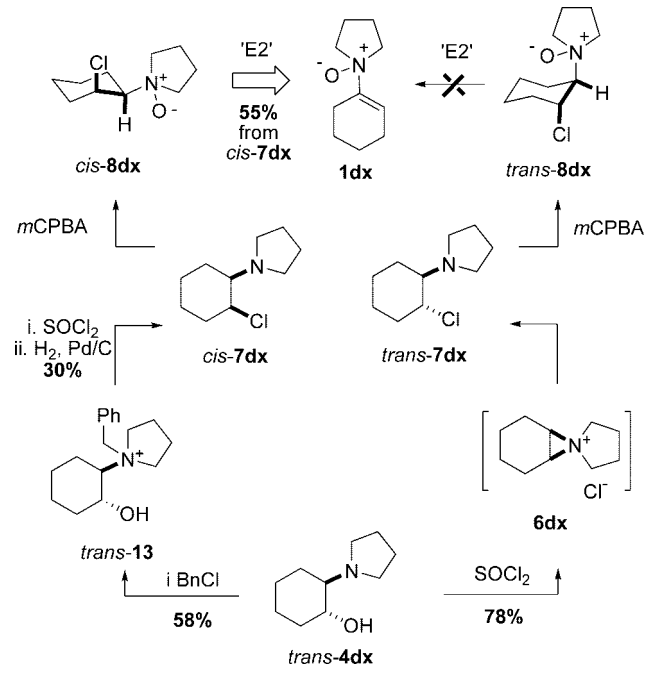
salts **8da** and **8dd** into alkoxyamine **12da** (67%) and a mixture of **11dd** (10%) and **12dd** (58%), respectively.

The choice of the leaving group appears crucial in this chemistry: due to their higher propensity to substitution, iodides, mesylates and tosylates are expected to be poorly suited leaving groups, favoring formation of intermediate **10**. Likewise, oxidation of β-(arylthio)amines to generate β-(arylsulfonyl)amines *N*-oxides was shown to be an equally inadequate strategy: fragmentation via a different pathway generates vinylsulfones and free amines.[26]

Spectroscopic differentiation between rearranged products **11**/**12** and the actual β-chloroamine *N*-oxides **8**[27] is often difficult but can be achieved by comparing the NMR signals of the alkyl groups adjacent to the *N*-oxide functionality: in our experience, for the *N*-oxides **8**, the ^{1}H NMR signals (typically δ = 3.20−4.80) are 1−1.5 ppm and the ^{13}C NMR signals (typically δ = 58.0−70.0) are 10−15 ppm higher than that of the corresponding amine.

Direct treatment of the crude salts **8** (containing a slight excess, 1.2−1.7 equiv,of stabilizing *m*-ClPhCO$_2$H) with excess KOBu^t in THF (0 °C to rt) leads to direct clean formation of the enamine *N*-oxides **1**. Upon scale-up of the deprotonation, reverse addition (i.e., addition of a THF solution of **8** to a suspension of excess KOBu^t in THF) was necessary to prevent competing "Owari-type" rearrangement. Removal of the THF under vacuum and CH_2Cl_2 extraction of the residue leads directly to **1**. This constitutes an attractive simplification over Richmond's original procedure (avoiding aqueous workup of **8**-like salts, subsequent water removal and drying, and final sublimation of **1**). Figure 2 shows the range of enamine *N*-oxides prepared by the new method.

SCHEME 2. Elimination of *trans*-Cyclohexyl β-Chloroamine *N*-Oxide vs Its *Cis* Analogue



Attempts to apply these conditions of HX elimination for the preparation of **1fa** (R^1 = CH_2Ph, R^2 = H) were unsuccessful, leading only to a complicated mixture. We believe that deprotonation at the benzylic position induces decomposition.

In most cases, the pure enamine *N*-oxides obtained during this work were crystalline, if highly hygroscopic, compounds. From an NMR-spectroscopic point of view, the olefinic part of the enamine *N*-oxides **1** does not clearly indicate the presence of an electron-withdrawing group (^{1}H: δ_α = 6.37−6.49, δ_β = 5.19−6.11; ^{13}C: δ_α = 137.0−148.3, δ_β = 107.8−139.4). However, the NMR criteria indicated above for the salts **8** provides a good indication of the presence of the desired *N*-oxide functionality: for the alkyl substituents around the *N*-oxide, δ_H = 3.18−3.48 and δ_C = 60.0−69.7. In the case of **1dd**, this connectivity was secured by the first X-Ray crystallographic structure of an enamine *N*-oxide (see the Supporting Information). Despite their hygroscopicity, and in contrast with earlier reports, exposure of these compounds to water did not result in any substantial hydrolytic degradation.

For the preparation of a cyclohexenyl derivative such as **1dx**, our assumption of an E2 elimination would require that only *cis*-substituted precursors were viable (such as *cis*-**8dx**, Scheme 2).

In the original literature,[7] the relative stereochemistry of the cyclic precursor β-chloro species used for **1** is not clear. We have explicitly prepared both relative stereoisomers in a racemic series starting from the pyrrolidine-opened epoxide product *trans*-**4dx**. Treatment of *trans*-**4dx** with thionylchloride afforded the *trans* β-chloro species **7dx** via the aziridinium **6dx**. After oxidation to *trans*-**8dx**, all attempts to engender elimination to **1dx** failed, and only decomposition processes akin to the formation of **10** were observed. In support of this notion, the tosylate of *cis*-**4dx** *N*-oxide failed to participate in the desired elimination (with either KOBu^t/THF or DBU/CH_2Cl_2). Cyclohexyl cis related β-chloroamines are a rare class of compounds. We prepared *cis*-**7dx** by preventing aziridinium formation through *N*-benzylation of *trans*-**4dx** with BnCl. Subsequent

(26) Griffin, R. J.; Henderson, A.; Curtin, N. J.; Echalier, A.; Endicott, J. A.; Hardcastle, I. R.; Newell, D. R.; Noble, M. E. M.; Wang, L.-Z.; Golding, B. T. *J. Am. Chem. Soc.* **2006**, *128*, 6012–6013.

(27) Analytical features of the salts **8**: (a) EI-MS: loss of the oxide is often observed, hence $[M-O]^{+\bullet}$ as a main peak; ESI-MS: $[M+H]^+$ is the main peak, confirming the expected formula. (b) Low chromatographic mobility on SiO_2 (elution with CH_2Cl_2/MeOH up to 70/30), whereas the corresponding products of the "Owari" rearrangement were eluted with Petrol−Et_2O mixtures. (c) TLC stains: 10% Ce(SO$_4$) in 15% aq H_2SO_4: blue spots; 2,3,5-triphenyltetrazolium chloride (TTC), 5 wt % in *i*-PrOH: pink spots.

(28) Analytical features of enamines *N*-oxides **1**: (a) MS: in ESI, small signals matching $[M+H]^+$ and $[M+Na]^+$, yet the main signal is $[2M+H]^+$ indicating propensity to form H-bridged homoconjugate dimers in solution. (b) Low chromatographic mobility on SiO_2 (elution with CH_2Cl_2/MeOH up to 70/30); c) TLC stains: Ce(SO$_4$): blue spots, TTC in *i*-PrOH: pink spots.

inversion of *trans*-**13** with $SOCl_2$ and removal of the benzyl protecting group without further purification afforded the desired *cis*-**7dx** but in low yield. Nevertheless, *cis*-**7dx** oxidized smoothly with *m*-CPBA to afford *cis*-**8dx**, which did eliminate smoothly with Bu^tOK in THF to fashion **1dx**.

In conclusion, we have presented user-friendly conditions for the synthesis of enamine *N*-oxides and brought new evidence of the mechanism of "Owari-type" rearrangements.

Experimental Section

***N*-Oxidation of Tertiary *β*-Chloroamines with *m*-CPBA: 1-(2-Chloro-4-phenylbutyl)pyrrolidine *N*-Oxide, 3-Chlorobenzoic Acid Salt (8dd).** To a solution of dried *m*-CPBA (85−95 wt %, 1.1−1.5 equiv) in CH_2Cl_2 (0.2 M), cooled with an ice−brine bath, was added the amine slowly (1 mL/min) via syringe. The mixture was then stirred while being allowed to warm to room temperature. After consumption of the starting amine was complete, the solvent was removed under reduced pressure to yield quantitative amounts of the *m*-chlorobenzoic acid salt (**8**) of the *β*-chloroamine *N*-oxide as a brown oil. In all cases, excess *m*-chlorobenzoic acid was the main contaminant; the excess *m*-chlorobenzoic acid was assessed by ^{1}H NMR to be between 0.2 and 0.7 equiv. The highly hygroscopic nature of these salts (**8**) limits their suitability for combustion analysis: IR ($CHCl_3$) ν = 3000, 1700, 1570, 1495, 1455, 1430, 1365, 1290, 1255, 1145, 1070, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.03 (t, J = 1.6, Ar2-H), 7.92 (dt, J = 7.8, 1.6, Ar6-H), 7.45 (dt, J = 7.8, 1.6, Ar4-H), 7.33 (t, J = 7.8, Ar5-H), 7.26−7.20 (m, 2″-H, 6″-H), 7.20−7.14 (3″, 4″, 5″-H), 4.90 (dddd, J = 9.1, 8.0, 4.6, 1.3, 2-H), 4.86 (dd, J = 13.9, 1.3, 1-H), 4.51−4.39 (m, 1H) and 4.11−3.94 (m, 1H) and 3.45−3.34 (m, 2H) (2′-H_2, 5′-H_2), 3.52 (dd, J = 13.9, 8.0, 1-H), 2.91 (ddd, J = 13.8, 9.9, 5.0, 4-H), 2.81 (ddd, J = 13.8, 9.5, 6.5, 4-H), 2.55−2.42 (m, 2H) and 2.14−2.04 (m, 2H) (3′-H_2, 4′-H_2), 2.25 (dddd, J = 13.9, 9.9, 6.5, 4.6, 3-Ha), 2.15 (dddd, J = 13.9, 9.5, 9.1, 5.4, 3-H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.0 ($ArCO_2$), 140.2 (C-1″), 135.8, 134.2 (Ar-1, Ar-3), 131.7, 130.0, 129.4, 127.9 (Ar-2, Ar-4, Ar-5, Ar-6), 128.7 and 128.6 (C-2″/C-6″ and C-3″/C-5″), 126.4 (C-4″), 73.0 (C-1), 69.5, 67.2 (C-2′ and C-5′), 55.1 (C-2), 38.7 (C-4), 32.1 (C-3), 22.3, 20.6 (C-3′ and C-4′); HRMS calcd for $C_{14}H_{21}ClNO^+$ ($[M + H]^+$) m/z 254.1306, found 254.1304.

Enamine *N*-Oxides by Dehydrochlorination of *β*-Chloroamine *N*-Oxides. To an ice-cold suspension of $KOBu^t$ (10.0 g, 3 equiv) in THF (0.6 M) was added dropwise a solution of the *m*-chlorobenzoic acid salt of *β*-chloroamine *N*-oxide **8dd** (13.3 g, 28.8 mmol) in THF (0.2 M). The mixture was stirred and allowed to warm to room temperature. After 7 h, the THF was removed in vacuo. The resulting solid was triturated in CH_2Cl_2/MeOH (80/20) and filtered over a short plug of neutral alumina. Concentration in vacuo and chromatography (SiO_2, CH_2Cl_2/MeOH from 95/5 to 70/30) afforded **1dd** (3.91 g) as a crystalline solid that became oily if exposed to atmospheric moisture: yield 67%; IR ($CHCl_3$) ν = 2975, 2465, 1720, 1680, 1660, 1625, 1605, 1560, 1495, 1455, 1380, 1265, 1240, 1030, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.29−7.24 (m, 2″-H/6″-H), 7.19−7.13 (m, 3″-H/5″-H, 4″-H), 6.49 (dt, J = 13.3, 7.5, 2-H), 6.03 (dt, J = 13.3, 1.4, 1-H), 3.42−3.36 (m, 2H) and 3.29−3.22 (m, 2H) (2′-/5′-H_2), 2.74 (t, J = 7.5, 4-H_2), 2.42 (qd, J = 7.5, 1.4, 3-H_2), 2.55−2.46 (m, 2H) and 2.01−1.92 (m, 3H) (3′-H_2/4′-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 140.9 (C-1″), 139.4 (C-1), 128.5 and 128.4 (C-2″/C-6″ and C-3″/C-5″), 126.2 (C-4″), 125.3 (C-2), 69.6 (C-2′/C-5′), 35.0 (C-4), 30.5 (C-3), 21.8 (C-3′/C-4′); HRMS calcd for $C_{14}H_{20}NO^+$ ($[M + H]^+$) m/z 218.1539, found 218.1556.

Acknowledgment. We thank the EPSRC for support through grant EP/025080/1 and EP/E030092/1. SW acknowledges valuable input from the COST D40 Innovative Catalysis Programme.

Supporting Information Available: Experimental details and characterization data for all compounds. NMR spectra (^{1}H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8002166