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## **Enamines from Terminal Epoxides and Hindered Lithium Amides**

David M. Hodgson,\* Christopher D. Bray, and Nicholas D. Kindon<sup>†</sup>

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road,

Oxford OX1 3TA, United Kingdom

Received December 17, 2003; E-mail: david.hodgson@chem.ox.ac.uk

Reactions of epoxides with lithium amides have been investigated in considerable detail.1 The conversion of epoxides to allylic alcohols is one important transformation mediated by lithium amides, and often proceeds by a  $\beta$ -elimination process.<sup>2</sup> Epoxides may also undergo  $\alpha$ -deprotonation by lithium amides. The resulting transient  $\alpha$ -lithiated epoxides, e.g., **1** (also called oxiranyl anions),<sup>3</sup> possess carbenoid character and typically undergo intramolecular C-H insertion.<sup>4</sup> In 1994, Yamamoto and co-workers described the rearrangement of terminal epoxides to aldehydes using lithium 2,2,6,6-tetramethylpiperidide (LTMP).<sup>5</sup> A deuterium-labeling study showed that the reaction proceeded by  $\alpha$ -deprotonation, and it was suggested that the aldehyde was obtained from the  $\alpha$ -lithiated epoxide by rearrangement to an enolate. In the present report we disclose that this reaction in fact proceeds, remarkably, by insertion of the  $\alpha$ -lithiated epoxide into the lithium amide, resulting in a new method for enamine synthesis. We also report on the alkylation chemistry of these hindered enamines.

$$\begin{array}{c} & & \\ C_{16}H_{33} \end{array} \xrightarrow{O} \begin{array}{c} LTMP \\ \hline THF \end{array} \left[ \begin{array}{c} C_{16}H_{33} \end{array} \xrightarrow{O} L^{1} \end{array} \right] \xrightarrow{O} C_{16}H_{33} \xrightarrow{O} C_{16$$

During our studies on the synthesis of *trans*- $\alpha$ ,  $\beta$ -epoxysilanes from terminal epoxides using LTMP and TMSCl in situ,<sup>6</sup> we repeated the reaction of 1,2-epoxyoctadecane with LTMP (2.5 equiv, THF, 25 °C, 16 h) described by Yamamoto.<sup>5</sup> In agreement with the latter work, we obtained octadecanal in 77% yield (lit.<sup>5</sup> 79%) after column chromatography (SiO<sub>2</sub>). However, the <sup>1</sup>H NMR spectrum of the crude product (following aqueous workup, but prior to column chromatography) did not show the expected characteristic signals of octadecanal; instead, it contained signals consistent with an *E*-olefin [<sup>1</sup>H NMR  $\delta$  5.78 (dt, J = 14 and 1 Hz, 1H), 5.30 (dt, J = 14 and 7 Hz, 1H)]. Purification of the crude product by filtration through SiO<sub>2</sub>, which had been previously stirred with Et<sub>3</sub>N for 12 h, gave enamine 2a in 78% yield. Enamine 2a could not be independently synthesized from octadecanal by standard condensation techniques.<sup>7</sup> However, enamine **2b** (Table 1, entry 1), prepared from 1,2-epoxypentane and LTMP by the same method used for 2a, could also be synthesized, albeit in only 32% yield, by the addition of commercially available n-BuMgCl to N-formyl-TMP8 according to the procedure of Hansson and Wickberg.9 NMR monitoring of the reaction between 1,2-epoxypentane and LTMP in THF- $d_8$  indicated formation of enamine **2b** was complete within 5 min; this experiment shows that enamine 2b does not form by condensation between pentanal and 2,2,6,6-tetramethylpiperidine (TMP) during the reaction workup stage. Addition of LTMP (1.5 equiv) to the lithium alkoxide of N-(2-hydroxyoctadec-1-yl)-TMP (THF, 25 °C, 1 h) did not give enamine 2a, the starting material being returned in quantitative yield instead; this experiment

demonstrates that enamine formation does not proceed via a simple epoxide ring-opening/elimination pathway.

By analogy with the formation of alkenes from epoxides and organolithiums,  $^{1a,10}$  a suggested reaction pathway for the formation of enamine **2a** from the lithiated epoxide **1** is shown below. Comparison of the <sup>7</sup>Li NMR spectra of the reaction between 1,2-epoxypentane and LTMP (1.95 equiv THF, 25 °C, 1 h) and of that between 1,2-epoxypentane and *n*-BuLi (1.95 equiv THF, 25 °C, 1 h), prior to aqueous workup, reveals that they contain the same lithium byproduct, presumably Li<sub>2</sub>O.<sup>10,11</sup>



Given the synthetic utility of enamines,<sup>7</sup> we sought to examine the scope of this new, previously unrecognized reaction (Table 1).

Table 1. Enamines 2 from Epoxides and LTMP



<sup>a</sup> Isolated yield. <sup>b</sup> 5 equiv of LTMP.

As well as epoxides bearing simple alkyl chains (entries 1,2), those possessing a range of functional groups could be used: olefinic and aryl substitution (entries 3,4), as well as suitably

 $<sup>^{\</sup>dagger}$  AstraZeneca R&D Charnwood Medicinal Chemistry, Bakewell Road, Loughborough, Leics LE11 5RH, U.K.

protected alcohols, amines, and ketones (entries 5-7) are tolerated. A bis-enamine (entry 8) was also formed.  $\beta$ -Disubstituted epoxides were found to be inert under these conditions.<sup>6,12</sup>

Due to the well-known problem of N-alkylation, there are few examples of C-C bond-forming reactions of aldehyde enamines with unactivated alkyl halides,<sup>7</sup> although this process expands the range of electrophiles that one could use in the synthesis of monoalkylated aldehydes. It has been shown by Curphey et al. that increasing steric bulk around nitrogen promotes C- over Nalkylation.<sup>13</sup> However, reaction of enamine **2b** with even reactive electrophiles such as MeI failed to yield a-substituted aldehydes in satisfactory yields (30%). For hindered enamines 2a-i the nitrogen lone pair and  $\pi^*$  orbital of the olefin may be orthogonal, as evidenced by the very small difference in chemical shift observed in the <sup>1</sup>H NMR spectra between the two olefinic protons (e.g.  $\Delta \delta_{\rm H}$ = 0.48 for **2b**).<sup>7c,14</sup>

Attention therefore focused on the use of other lithium amides that would facilitate enamine formation from epoxides and where the enamine would be capable of reacting with electrophiles. Aside from LTMP, LiNCy<sub>2</sub> has been reported to rearrange epoxides to aldehydes, albeit in lower yields.<sup>5</sup> Although we were unable to isolate the enamine derived from 1,2-epoxyhexane and LiNCy<sub>2</sub>, reaction with the lithium amide LTBIPA derived from commercially available N-tert-butylisopropylamine produced enamine 3a in 42% yield. Traces of the 1,2-amino alcohol derived from direct epoxide ring opening were also observed.<sup>5,15</sup> The use of other solvents (e.g., Et<sub>2</sub>O, hexane) or the addition of additives (e.g., TMEDA, LiCl) did not increase the yield of enamine 3a. It is interesting to note that the difference in chemical shift observed in the <sup>1</sup>H NMR between the olefinic protons of enamine **3a** ( $\Delta \delta_{\rm H} = 1.45$ ) approaches that more typical of aldehyde enamines  $(\Delta \delta_{\rm H} \approx 1.5 - 2.0)$ .<sup>7c,14</sup>

## Table 2. Alkylation of Enamines 3a and 3b



entry	enamine	electrophile (R <sup>2</sup> X) <sup>a</sup>	temp (° C)	time (h)	yield (%) <sup>b</sup>	
1	3a	PhCH <sub>2</sub> Br	15	18	4a	>99
2	3a	CH <sub>3</sub> CH=CH <sub>2</sub> Br	15	18	4b	96
3	3a	MeO <sub>2</sub> CCH <sub>2</sub> Br	15	16	4c	91
4	3a	$HC \equiv CCH_2Br$	15	15	<b>4d</b>	>99
5	3a	acrylonitrile	84	19	4e	91
6	3a	methyl acrylate	84	22	<b>4f</b>	70
7	3a	MeI	15	18	4g	86
8	3a	EtI	50	18	4 <b>h</b>	99
9	3a	<i>n</i> -BuI	75	23	<b>4i</b>	97
10	3a	$C_{10}H_{21}I$	84	22	4j	95
11	3a	<i>i</i> -PrI	84	40	4k	80
12	3b	<i>n</i> -BuI	84	96	<b>4i</b>	84
13	3b	i-PrI (3 equiv)	94	96	4k	49

<sup>a</sup> 2 equiv unless otherwise stated. <sup>b</sup> Isolated yield of aldehyde following acid hydrolysis (NaOAc:AcOH:H2O; 1:1:2), aqueous workup and column chromatography.

Enamine 3a reacted with a variety of activated alkyl halides and electron-deficient olefins to give a range of  $\alpha$ -substituted aldehydes in excellent yields (Table 2, entries 1-6), indicating that, despite being highly hindered, it had retained its nucleophilic nature. Moreover, enamine 3a reacted not only with MeI and EtI (Table 2, entries 7 and 8) in excellent yields, but also with 1-iodobutane, 1-iododecane, and even 2-iodopropane (entries 9-11). Next, we sought a lithium amide whose steric hindrance was intermediate in nature between that of LTBIPA and LTMP. Upon reaction with 1,2-epoxyhexane, lithium *N-tert*-butylpinacoylamide<sup>16</sup> (2.5 equiv THF, 25 °C, 16 h) was found to produce enamine 3b in 58% yield (NCH=CH;  $\Delta \delta_{\rm H} = 0.89$ ); this could subsequently be alkylated with 1-iodobutane (entry 12) and 2-iodopropane (entry 13). Entries 9-13 represent the first examples of enamines reacting with such unreactive electrophiles in synthetically useful yields.

In conclusion, we have uncovered a new reactivity mode of lithium amides with epoxides which leads to hindered enamines and have demonstrated that some of the latter are capable of reacting with unactivated primary and secondary alkyl iodides. That hindered lithium amides react as nucleophiles with  $\alpha$ -lithiated epoxides serves to emphasize the high electrophilicity of these carbenoids.<sup>17</sup>

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Supporting Information Available: Experimental procedures and NMR spectra of 2a-i, 3a-b, 4a-k, and details regarding starting epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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