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**LIC-KOR Promoted Nitrone Reactivity: Stereoselective Synthesis of Highly Conjugated Imines and Secondary Amines.**

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[[1]](#footnote-2)One of the most intriguing problems involved in metalation processes concerns the possibility of combining high basicity and high selectivity, that could be considered as mismatching terms. Schlosser-Lochmann mixed bases also called “Li-K mixed bases” or “superbases” perfectly fit into this definition. Superbases, easily prepared mixing 1 or 2 eq. of Na or K alkoxide with a solution of alkyllithium, were discovered by Avery Morton in 1946,1 and then developed by Schlosser and Lochmann2-4 who demonstrated their peculiar synthetic properties in the removal of allylic, benzylic, vinylic and cyclopropylic protons.5-7 For several years our research group has been studying the reactivity of α,β-unsaturated acetals as masked acyl anions, in the presence of Li-K mixed bases. As a matter of fact, these substrates react with organolithium derivatives showing several reactivity patterns depending on their structure and reaction conditions.8-13 When reacted in a superbasic medium they afford functionalised alkoxy-1,3-dienes in a regio- and stereoselective manner, as reported in Scheme 1.14, 15



Scheme 1 General conditions for the synthesis of functionalised alkoxy-1,3-dienes from α,β-unsaturated acetals in the presence of Li-K mixed superbases.

The reaction has been extended to cyclic α,β-unsaturated acetals, and several electrophiles have been used such as alkyl halides, carbonyl compounds and carboxylic acids,16 more recently the synthetic approach has been exploited to obtain enantiopure sulfinimines,17 α-ketoimides, γ-lactams and cyclic iminoethers.18 Moreover, when boron and tin derivatives were used, the so obtained intermediates readily cross-couple following a Suzuki or Stille procedure.19, 20 Finally, the functionalised alkoxydienes have been exploited as substrates for Heck couplings.21, 22 In this paper we wish to present our preliminary results on the reactivity of *N*,α-diarylnitrones with alkoxydienes in the presence of Schlosser-Lochmann superbases. Nitrones, which could be considered as imine *N*-oxides, are characterised by a C-N double bond and a N-O single bond. The structure exhibits a charge separation where the negative charge is localised on the oxygen and the positive can either be on N or C atom (Figure 1).



**Figure 1** General structure of nitrones

This dipolar character, coupled with the imine functionality, makes nitrones very interesting substrates not only in organic chemistry,23 but also in medicinal chemistry24-26 and polymer science applications.27, 28 Use of nitrones as 1,3-dipoles in [3 + 2] dipolar cycloadditions with electron-poor alkenes, allenes, alkynes and Fisher metal-carbene complexes is well known.29-36 Moreover, several examples of nucleophilic addition to nitrones have been reported.37-41 Reissig *et al.* reported an interesting addition of chiral nitrones to lithium alkoxy allenes affording 1,2-oxazines which are suitable intermediates for the synthesis of amino sugars.42, 43 The stereoselective synthesis of epoxyaminoacids by reaction of oxazolinyloxiranyllithiums with nitrones has also been described.44

**Results ans discussion**

Preliminary attempts to test the reactivity of nitrones with α,β-unsaturated acetals in superbasic medium were accomplished with the commercially available *N-tert*-butyl-α-phenylnitrone **1** (Figure 2) but no reaction was observed and the unreacted nitrone was each time recovered. Diverse experimental conditions such as a different ratio of LIC-KOR equiv. in respect to the nitrone and acetal, reaction temperatures and different time did not afford any addition product, leaving the nitrone unreacted. As a consequence, we turned our attention to the more electrophilic α*,N*-diphenylnitrone **2a** (Figure 2).



**Figure 2** *N-tert*-butyl-α-phenylnitrone **1** and α*,N*-diphenylnitrone **2a**

We were delighted to observe that under the same experimental conditions previously used for nitrone **1,** the reaction was completed in 2 hours. The TLC monitoring of the reaction progress indicated the disappearance of the starting nitrone. The characterisation of the product evidenced the presence of a quaternary carbon at 162 ppm in the 13C NMR spectrum and a molecular weight of 277 AMU. The spectroscopic characterisation was coherent with the formation of the imine **4a** represented in Scheme 2. We hypothesised a cascade process where the addition of the nitrone **2a** to the alkoxydienyl anion is followed by the elimination of a hydroxyl species with the formation of an imine by a E1cb process (Scheme 2). This could be reasonably promoted by LIC-KOR base on the intermediate **A** which appears to be unstable in superbasic medium, as witnessed by the formation of the imine **4a** instead of the expected corresponding *N*-hydroxylamine. To our knowledge this type of reactivity of α*,N*-diarylnitrones, which is ascribable to the presence of the LIC-KOR base, has never been reported. Moreover, it has to be noticed that this domino process allows a highly conjugate imine to be obtained.



**Scheme 2** Hypothesised mechanism for the formation of α,*N*-diphenyldienyloxyimine

The reaction of crotonaldehyde diethyl acetal (**3**) with α*,N*-diphenylnitrone **2a** was selected as model reaction in order to optimise the process. This was done by evaluating the effect of the base, both as type and number of equivalents, reaction temperature and time respectively. The results are reported in Table 1.

**Table 1**

Optimisation of the reaction between crotonaldehyde diethyl acetal (**3**) and α*,N*-diphenylnitrone (**2a**) a

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Base | Eq. | Exp. cond.b | Yieldc |
| 1 | LIC-KOR | 2.2 | 3h, -95°C | < 1% |
| 2 | LIC-KOR | 2.2 | 1h, -95°C→  r.t., 2.5 h | 16% |
| 3 | LIC-KOR | 4.0 | 2h, -95°C→  0°C, 2.5 h | 0% |
| 4 | LIC-KOR | 2.2 | 0.5h, -95°C→  r.t., 72 h | 0% |
| 5 | LIC-KOR | 2.2 | 0.5h, -95°C→  0°C, 2 h | 24% |
| 6 | LIC-KOR | 2.2 | 0.5h, -95°C→  -30°C, 2 h | < 1% |
| 7 | LIC-KOR | 3.0 | 0.5h, -95°C→  0°C, 2 h | 26% |
| 8 | LIC-KOR | 3.0 | 0.5h, -95°C→  0°C, 3 h | 28% |
| 9 | **LIC-KOR** | **3.0** | **0.5h, -95°C→**  **-20°C, 3 h** | **32%** |
| 10 | LIC-KOR | 3.2 | 0.5h, -95°C→  0°C, 3 h | 12% |
| 11 | LIDAKOR | 3.2 | 0.5h, -95°C→  0°C, 3 h | < 1% |

*a* Reaction conditions: crotonaldehyde diethyl acetal **3** (1 mmol), anhydr. THF 1 eq. nitrone **2a**. *b* The experimental conditions refer to the period after the nitrone addition. *c* Isolated products, purified by column chromatography.

First of all, the role of temperature was evaluated. Whereas the first part of the reaction was always conducted at -95°C, attention was paid to the temperature and reaction times after the nitrone addition. When the reaction was carried out at -95°C the unreacted nitrone was recovered at the end of the reaction (entry 1), whereas when the temperature was increased to r.t. for 2.5 h a 16% yield (entry 2) was obtained. The yield dropped to 0% carrying out the reaction at r.t. for 72 h, probably due to the decomposition of the reagents and/or products (entry 4). We slightly changed the temperature after the nitrone addition and observed that up to -30°C the rate of the process was negligible and the product was recovered only in traces (entry 6); we obtained better results increasing the reaction temperature at 0°C, in this case the product was recovered with 24% yield (entry 5). Then we evaluated the influence of the base equivalents and, according to the mechanism proposed in Scheme 2, we considered 3 equiv of base (entries 7-8). We obtained 24 and 26% yield respectively. When we used a greater amount of base, 3.2 and 4 eq on the contrary, the yields decreased to 12 and 0% probably because of degradation processes (entries 10 and 3). Finally we analysed the influence of the base and we carried out the reaction using the LIDAKOR base, which is an equimolar mixture of *iso*Pr2NH, *n*-BuLi and *tert*-BuO-K+ and is a weaker base in respect to LIC-KOR (entry 11). In this case no product formation was observed. Finally we evaluated the conditions indicated in entry 9 as the best found. After the addition of the nitrone, the reaction was maintained at -95°C for 0.5 h, then the temperature was allowed to raise to -20°C for 3 h. At this temperature the yield was slightly improved, maybe because of the reduction of the degradation phenomena. Once set the optimal conditions, the scope of the reaction was evaluated. To this purpose we prepared several α*,N*-diarylnitrones by the acid catalysed condensation of the suitable substituted benzaldehyde with *N*-phenylhydroxylamine. Nitrones were obtained with yields comparable to those reported in literature (see supporting information).45 The results of the reaction between crotonaldehyde diethyl acetal (**3**) with α-aryl*-N*-phenylnitrones **2a**-**2h** are shown in Table 2. As expected the presence of substituted aromatic rings linked to the azomethyne carbon of the nitrone greatly influenced its reactivity, especially in terms of reaction times. *Para*-electrondonating groups on the α- phenyl ring are expected to stabilise the positive charge in the nitrone, thus reducing its electrophilicity and reactivity. When α-(4-*N,N*-dimethylaminophenyl)-*N*-phenylnitrone **2g** and α-(4-methoxyphenyl)-*N*-phenylnitrone **2h** are used (entries 7 and 8), only traces of the desired product are observed, whereas the presence of a weaker electrondonating substituent such as methyl (entry 2, nitrone **2b**) affords the imine **4b** in 6h with a 25% yield. Imine **4c** and **4d** are obtained in shorter times (2.5 and 2h respectively, 25 and 27% yield) when 4-bromo (**2c**) and 4-chloro (**2d**) derivatives are used (entries 3 and 4). On the contrary, when electron-withdrawing substituents are present, the reaction is favoured. This is confirmed by the fact that when the halogen is in *meta* position, the (*Z*, 2*E*)-2-ethoxy-*N*-phenyl-1-(3-chlorophenyl)-penta-2,4-dien-1-imine (**4e**) is recovered in 2 h. Finally an heterocyclic derivative has been prepared, but the presence of the electron-poor pyridyl ring does not induce any activation on the nitrone, and the corresponding imine **4f** has been obtained with a low yield (entry 6).

**Table 2**

(*Z*, 2*E*)-2-Ethoxy-*N*-phenyl-1-arylpenta-2,4-dien-1-imine (**4a**-**4f**) obtained by reaction of crotonaldehyde diethyl acetal (**3**) and nitrones **2a**-**2h**.

|  |  |  |
| --- | --- | --- |
|  | **Nitrone** | **Iminea** |
| **1** |  |  |
| **2** |  |  |
| **3** |  |  |
| **4** |  |  |
| **5** |  |  |
| **6** |  |  |
| **7** |  |  |
| **8** |  |  |

**a** Isolated products, purified by column chromatography.

As can be observed, the domino process here described allows the unsaturated imine to be obtained in a complete stereoselective manner, where the C-C double bond has an *E* configuration whereas the imine group shows a *Z* configuration. The geometry of the two double bonds has been determined by a NOESY experiment carried out on the derivative **4f**, where the phenyl and pyridine protons have different chemical shifts (6.8-7.5 ppm and two doublets at 8.0 and 8.75 respectively). In the NOESY of (*Z*, 2*E*)-2-ethoxy*-N*-phenyl-(1-pyridin-4-yl)-penta-2,4-dien-1-imine **4f** (reported in the supporting information) we can observe two correlation spots, the first clearly indicates a spatial interaction between the methylenic group of the ethoxy moiety (3.83 ppm) and the β-proton to the imine group (5.50 ppm), thus indicating the *E* geometry of the C-C double bond (see Figure 3, left). The second shows a correlation between the γ-proton in respect to the C-N double bond (5.95 ppm) and the phenyl protons (7.00 ppm), consistent with a Z configuration, (see Figure 3, right).



**Figure 3** Spatial correlation between protons to evidence the configuration of the C-C and C-N double bonds

At this point the imines **4a – 4h** were hydrolysed under acidic conditions, in order to regenerate the carbonyl functionality according to an umpolung strategy. The hydrolyses were accomplished at r.t. in CHCl3 overnight using 10 meq of Amberlyst 15® as proton source. The 1H NMR analysis of the product suggested the formation of a chiral cyclic structure, as evidenced by the presence of two doublets which resonate at 3.2 and 3.5 ppm pertinent to endocyclic diastereotopic methylene protons. We hypothesised a process where a proton attacks the imine double bond to afford a carbocation which is benzylic, allylic and α to a nitrogen at the same time (A, Scheme 3), followed by an intramolecular electrophilic addition to the terminal double bond of the dienic portion (B, Scheme 3), finally the elimination of ethanol leads to the corresponding 2-phenylamino-α,β-cyclopentenone.



**Scheme 3** Synthesis of 5-aryl-5-arylaminocyclopent-2-enones **5a - 5e** by acid catalyzed hydrolysis

Cyclopentenones, which are versatile building blocks for the preparation of structurally diverse biologically active molecules, have been found in various natural products and pharmaceuticals and applied as useful building blocks in organic synthesis.46-48 Enones **5a**-**5e** were obtained in good yields, also in this case the effect of the substituents is evident, the presence of halogens in *meta* and *para* position leads to better yields thanks to the increase of the carbocation intermediate reactivity. Hydrolysis was also attempted on the pyridyl intermediate **4f** but no product was recovered, probably because of the formation of the corresponding pyridinium salt. The structure was completely elucidated, on the base of the COSY and NOESY spectra (see supporting information).

In conclusion, in this paper preliminary results on the ability of metalated-1-alkoxydienes to react with nitrones in the presence of LIC-KOR superbase are presented. A domino process, where an E1cb reaction follows the addition of nitrone to the metalated intermediates, permits the totally stereoselective synthesis of 2-ethoxy-*N*-phenyl-1-arylpenta-2,4-dien-1-imines. At our knowledge, this type of elimination, promoted by the superbasic medium on a hydroxylamine has never been observed. Moreover when the imines are hydrolysed in the presence of the resin Amberlyst 15® to unmask the original carbonyl function, peptidomimetic functionalised 5-aryl-5-phenylaminocyclopentenones are obtained in good yields.

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Supplementary Material General procedure for the preparation and spectroscopic characterisation of 2a-2h, 4a-4f, 5a-5e are reported. NMR spectra of 4a-4f, 5a-5e are included.

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49 **General procedure for the reaction of α,β-unsaturated acetals and α,*N*-diaryl nitrones in the presence of LIC-KOR superbase.** In a Schlenk bottlecontaining anhydr. THF, sublimed *t-*BuO-K+ (3.0 mmol, 0.34 g) was suspended, then (*E*)-but-2-enal diethyl acetal was added dropwise (1 mmol) and the solution was cooled to -95°C. After 5 min. *n*BuLi was carefully added (3.0 mmol, 1.9 mL), the solution turned red and was stirred at -95°C for 2 h. Then the suitable α,*N*-diarylnitrone was added (1 mmol) and the solution turned to dark violet, after 0.5 h the temperature was increased and maintained at -20°C until the disappearance of the nitrone observed by TLC (EP/EE 50/50). Then H2O was added and the mixture was extracted with Et2O (2 X 20 mL), then washed with brine (2 X 20 mL), dried **(**K2CO3**),** filteredand evaporated under reduced pressure. **4a:** After chromatographic purification (EP/EE 90/10) a pale yellow oil was obtained (88 mg, 32%). Found C, 82.27; H, 6.88; N, 5.04%. Calc. for C19H19NO: C, 82.28; H, 6.90; N, 5.05%. ʋmax(neat)/cm-1 2978, 1592, 1483, 1165, 686. δH (200 MHz; CDCl3, Me4Si) 1.24 (3H, t, *J* = 7.0 Hz, C*H*3CH2O), 3.75 (2H, q, *J* =7.0 Hz, CH3C*H*2O), 4.78 (1H, dd, *J* =10.2, 1.7 Hz, *H*CH=C), 4.92 (1H, dd, *J* =16.6, 1.7 Hz, *H*CH=C), 5.42 (1H, d, *J* =10.9 Hz, C*H*=COEt), 6.05 (1H, dt, *J* =16.6,10.9 Hz, CH2C*H*-CH), 6.92 (2H, d, *J* =8.4 Hz, Ar), 7.10 (1H, t, *J* =7.3 Hz, Ar), 7.20-7.70 (5H, m, Ar), 7.98 (2H, d, *J* =8.4 Hz, Ar); δC (50.2 MHz; CDCl3, Me4Si) 14.3 (CH3), 63.2 (CH2), 104.7 (CH), 113.5 (CH2), 119.6 (CH2), 123.8 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 130.9 (CH), 131.7 (CH), 136.6 (Cq), 150.8 (Cq), 151.8 (Cq), 162.7 (Cq). MS (ESI): *m/z* = 278 [M + H]+.

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