# N-Metalated imines by reaction of 1,1-diethoxybut-2-ene with aromatic nitriles, as useful intermediates for the synthesis of substituted pyrimidines and cyclopentenones†‡

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A new approach to the synthesis of pyrimidines and cyclopentenones is described. The method exploits the reactivity of α,β-unsaturated acetals with aromatic nitriles in the presence of the Schlosser's superbase LIC-KOR.

The synthetic community dedicates much effort to the investigation of new approaches to those derivatives that are related to the synthesis of natural products, pharmaceuticals, and functional materials. Among these, pyrimidines and cyclopentenones play a significant role. Most of the synthetic routes to pyrimidine derivatives usually involve methodologies based on the condensation reaction of 1,3-dicarbonyl compounds with amidines (Pinner synthesis),[1] or with an aryl aldehyde and urea (Biginelli synthesis).[2] Moreover, recent approaches to substituted derivatives exploit cross-coupling chemistry.[3] Recently, it has been reported that the trapping of highly activated amide derivatives with weakly nucleophilic nitriles directly provides the corresponding pyrimidine derivatives.[4] Equally significant is the development of synthetically useful methods for the preparation of cyclopentyl derivatives. In particular, cyclopentenones exhibit characteristic biological activity and are useful for the versatility of their chemical features, and for their application in natural product synthesis. The methods reported for the cyclopentenone ring formation mainly involve the intramolecular aldol reaction of suitable 1,4-dicarbonyl compounds,[5] Nazarov cyclization of dienones,[6] insertion reaction of an intermediate alkylidene carbene,[7] Pauson–Khand reactions,[8] and the tandem Michael addition–carbene insertion reactions of a β-ketoethynyl (phenyl)-iodonium salts.[9] Among the various syntheses for N-containing heterocycles, the addition of organolithium reagents to nitriles provides an alternative and fundamental synthetic method. In this context, 2-arylpyrroles have been prepared from 2-lithio-N,N-dibenzylcyclopropylamine and nitriles,[10] while a novel cycloaddition reaction of aromatic nitriles with monolithio- and dilithiobutadienes has been developed in order to synthesize substituted pyridines and pyrroles.[11]
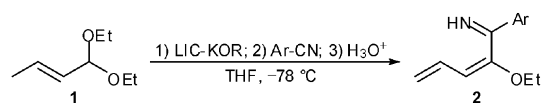
Herein we would like to report a novel and synthetically useful reaction pattern of 1,1-diethoxybut-3-ene with nitriles in the presence of Schlosser's superbase LIC-KOR,[12] that afford N-containing heterocycles as the final products. Moreover, highly functionalized cyclopentenones can be also isolated by slightly modifying the synthetic procedure.

Metalation of 1,1-diethoxybut-2-ene 1 with 3 equiv. of LIC-KOR base afforded the (1-ethoxybuta-1,3-dienyl)metal (metal = Li or K) as a purple red solution.[13] Addition of 1 equiv. of a nitrile to the above reagent caused the addition reaction and the color was discharged within a few seconds. The reaction mixture was then stirred at −78 °C for 2 h, and the expected imine 2 was isolated, as the E pure isomer, in high yield upon quenching at this temperature (Scheme 1).§

In Table 1 are reported the results concerning the preparation of various imine derivatives.

In order to direct the reaction pattern towards new pathways, we have then investigated different experimental conditions. We were especially interested in promoting the trapping of the metalated imine intermediate, that can be in principle be accomplished according to an intra- or intermolecular approach. During this systematic investigation we envisioned that a new three-component synthesis of the pyrimidine ring could be planned on the basis of the disconnection approach shown in Scheme 2, that hints the use of a metalated diene as a nucleophile and of two nitriles as electrophiles (1,6-, 2,3-, and 4,5-bond forming reactions).

When the crotonaldehyde acetal 1 was reacted under nitrogen with 2 equiv. of benzonitrile in THF for 2 h at −78 °C in the presence of the LIC-KOR base, and then for 2 h at room temperature, 5-ethoxy-2,4-diphenyl-6-vinylpyrimidine (7, Ar = Ph) was produced in 80% yield. As illustrated in Scheme 3, the initially formed N-metalketimine 3, as the reaction temperature increases, adds to a second molecule of organonitrile and gives a new N-metalketimine intermediate 4. Finally, an intramolecular cyclization leads to the metal 5-ethoxy-2,6-

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† Electronic supplementary information (ESI) available: Characterization data for all products, copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds. See DOI: 10.1039/b719462e
‡ Partially taken from the PhD research project of MB.



Scheme 1 Generation and reaction of 1-ethoxybuta-1,3-diene with nitriles affording imine derivatives.

**Table 1**  Synthesis of imines starting from 1,1-diethoxybut-2-ene **1**[a]

| Nitriles | Product | Yield[b] (%) |
|---|---|---|
| PhCN | HN=Ph, OEt | 72 |
| Me-C6H4-CN | HN=Tol, OEt | 47 |
| MeO-C6H4-CN | HN=C6H4OMe, OEt | 84 |
| Py-CN | HN=Py, OEt | 82 |
| (CH3)3C-CN | HN=CMe3, OEt | 82 |

[a] Reaction conditions: *t*-BuOK (3.0 equiv.); BuLi (3.0 equiv.); **1** (1.0 equiv.); THF (20.0 mL); . [b] Isolated yield.

diphenyl-4-vinyl-4*H*-pyrimidin-1-ide intermediate (**5**, Ar = Ph), which upon quenching with aqueous NH₄Cl affords pyrimidine **7**, probably *via* aerial oxidation¶.‖

The synthesis was successfully carried out with benzonitrile and with aryl nitriles bearing electron donating and electron withdrawing substituents. The results obtained using different organonitriles are reported in Table 2.

Successively, to examine a broader synthetic applicability of the *N*-metalketimine, we attempted the acidic hydrolysis of both the enol ether and iminic function of ketimine intermediate **2**, in order to obtain 1,2-dicarbonyl derivatives. Unfortunately, after treatment with Amberlyst-15 in wet CHCl₃, or with aqueous 1N HCl (H₂O : THF = 1 : 1), only the product of imine hydrolysis was recovered.**

Finally, in order to tune the reactivity of imine group, we examined the trapping of the *N*-metalketimine intermediate with benzoyl chloride, followed by acidic hydrolysis with Amberlyst-15 in wet CHCl₃. Reaction yield, and products

**Table 2**  Synthesis of pyrimidines **7** starting from **1**[a]

| Reactant | Product | Yield[b] (%) |
|---|---|---|
| PhCN | Ph-N-Ph pyrimidine, OEt, vinyl | 65 |
| Me-C6H4-CN | Tol-N-Tol pyrimidine, OEt, vinyl | 63 |
| MeO-C6H4-CN | MeOC6H4-N-C6H4OMe pyrimidine, OEt, vinyl | 74 |
| Py-CN | Py-N-Py pyrimidine, OEt, vinyl | 81 |
| F3C-C6H4-CN | F3CC6H4-N-C6H4CF3 pyrimidine, OEt, vinyl | 65 |

[a] Reaction conditions: *t*-BuOK (3.0 equiv.); BuLi (3.0 equiv.); **1** (1.0 equiv.); THF (20.0 mL); ArCN (2.5 equiv.). [b] Isolated yield.
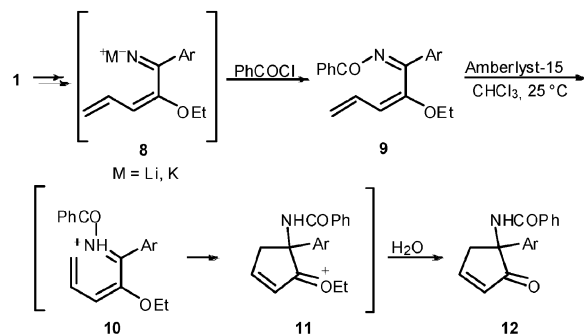


**Scheme 4**  Synthesis of substituted cyclopentenones.
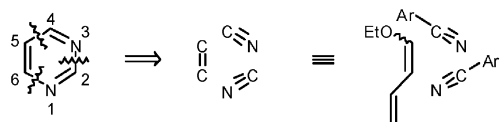


**Scheme 2**  Disconnection approach resulting in a three-component pyrimidine synthesis.
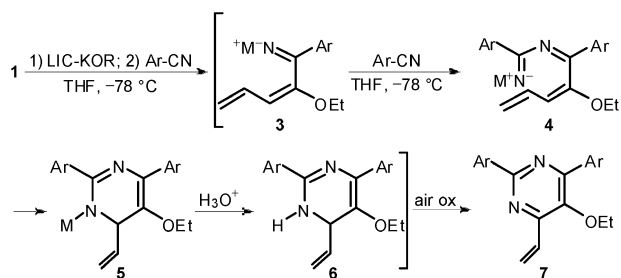


**Scheme 3**  One-pot synthesis of substituted pyrimidine derivatives.

**Table 3**  Synthesis of protected dienyl imines **9**[a] and substituted cyclopentenones **12**[b] starting from **1**

| Nitriles | Product **5** (Yield %)[c] | Product **6** (Yield %)[c] |
|---|---|---|
| PhCN | PhCO-N=Ph, OEt, vinyl | NHCOPh, Ph cyclopentenone (92) |
| MeO-C6H4-CN | (64) | NHCOPh, C6H4OMe cyclopentenone (95) |
| (CH3)3C-CN | PhCO-N=CMe3, OEt, vinyl (72) | NHCOPh, CMe3 cyclopentenone (0) |

[a] Reaction conditions: *t*-BuOK (3.0 equiv.); BuLi (3.0 equiv.); **1** (1.0 equiv.); THF (20.0 mL); ArCN (1.1 equiv.); PhCOCl (2.2 equiv.). [b] **5** (0.5 mmol); CH₂Cl₂ (2 mL); Amberlyst-15 (cat.). [c] Isolated yield.

obtained according to the mechanism proposed in Scheme 4, are reported in Table 3.††‡‡

In summary, a new synthesis for a series of derivatives of potentially valuable biological interest has been developed by the one-pot reaction of an α,β-unsaturated acetal with aromatic nitriles in the presence of LIC-KOR superbase.

## Notes and references

§ *General procedure for the syntheses of dienyl imines* **2**: a solution of freshly sublimated *t*-BuOK (6 mmol, 672 mg, 3.0 equiv.) in 20 mL of THF was refrigerated to −78 °C under nitrogen. 1,1-diethoxybut-2-ene **1** (2 mmol, 288 mg) in 2 mL of THF and BuLi (1.6 M in hexanes, 6 mmol, 3.75 mL, 3.0 equiv.) were then quickly added and the mixture was stirred for 2 h. During this time the temperature was allowed to raise to −40 °C. Afterwards the reaction was cooled again to −78 °C and the appropriate nitrile (2.2 mmol, 1.1 equiv.) in 5 mL of THF was added. The resulting mixture was stirred at −78 °C for 1 h. Then, a saturated $NH_4Cl$ aqueous solution (20 mL) was added, the mixture extracted with $Et_2O$ (3 × 20 mL), the organic layers collected, washed with $H_2O$ (10 mL), brine (2 × 20 mL), and dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, the crude products were purified by flash column chromatography.
¶ The last step of mechanism, namely the conversion of dihydropyrimidine **6** into pyrimidine **7**, could be perhaps as well attributed to metal hydride elimination, as proposed by Z. Xi and colleagues in the articles that we have quoted in ref. 11. At the moment we have no experimental evidence in order to support such an hypothesis.
‖ *General procedure for the syntheses of pyrimidines* **7**: the procedure in detail follows what specified for the preparation of imines **2**, up to the generation of metalated 1-ethoxybuta-1,3-diene. Afterwards the reaction was cooled again to −78 °C and a solution of the appropriate nitrile (5.0 mmol, 2.5 equiv.) in 5 mL of THF was added. The resulting mixture was stirred at −78 °C for 1 h, after which the temperature was allowed to raise to rt and the reaction stirred overnight. Then, a saturated $NH_4Cl$ aqueous solution (20 mL) was added, the mixture extracted with $Et_2O$ (3 × 20 mL), the organic layers collected, washed with $H_2O$ (10 mL), brine (2 × 20 mL), and dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, the crude products were purified by flash column chromatography.
** Probably derivatives **2** do not release both masked carbonyl functions since an unstable charged intermediates has to be considered inspecting the mechanistic hydrolysis path.
†† *General procedure for the syntheses of protected dienyl imines* **9**: the procedure in detail follows what specified for the preparation of imines **2** up to the genration of metalated 1-ethoxybuta-1,3-diene. Afterwards the reaction was refrigerated again to −78 °C and a solution of the appropriate nitrile (2.2 mmol, 1.1 equiv.) in 5 mL of THF was added. The resulting mixture was stirred at −78 °C for 1 h, then PhCOCl (4.4 mmol, 2.2 equiv.) was added dropwise. Then, a saturated $NH_4Cl$ aqueous solution (20 mL) was added, the mixture was extracted with $Et_2O$ (3 × 20 mL), the organic layers collected, washed with $H_2O$ (10 mL), brine (2 × 20 mL), and dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, the crude products were purified by flash column chromatography. ‡‡ *General procedure for the syntheses of cyclopentenones* **12**: a solution of protected dienyl imine (0.5 mmol) in $CH_2Cl_2$ (2 mL) was stirred in the presence of Amberlyst-15® and the reaction progress monitored by TLC. When the reaction was complete, a small amount of anhydrous $K_2CO_3$ was added. After

filtration and evaporation of the solvent, the crude products were purified by column flash chromatography.

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