Unconventional oxazole formation from isocyanides†

Aurélie dos Santos, Laurent El Kaïm,* Laurence Grimaud* and Caroline Ronsseray

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The coupling of an acyl chloride with an isocyanide affords 2,5-disubstituted oxazoles under mild basic conditions instead of 4,5-disubstituted derivatives when using Schöllkopf conditions (butyllithium); this reaction constitutes a remarkable example of a base-induced chemoselective process in isocyanide chemistry.

Over the last twenty years, a large number of compounds bearing an oxazole nucleus have been isolated from diverse marine sources, as well as from the fermentation broth of numerous bacteria.[1] Besides the biological relevance of these compounds, the interest in oxazoles is mostly associated with the moderate stabilization of their aromatic ring and their consequent use as synthetic intermediates towards other heterocyclic families or aliphatic compounds.[2] The traditional preparation of oxazoles by the dehydration of α-acylaminocarbonyls (Robinson–Gabriel type reactions)[3] has, following the pioneering studies of the groups of Van Leusen[4] and Schöllkopf,[5] been greatly enriched by strategies using isocyanides (Scheme 1).

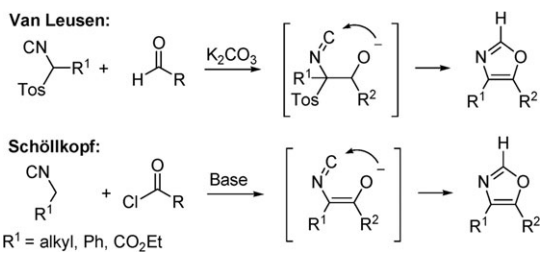
When considering the Schöllkopf reaction, though the isocyanide moiety increases the acidity of the vicinal proton, strong bases such as *n*-BuLi or LDA are still needed to perform the deprotonation of the alkyl and benzyl isocyanide and the subsequent attack on the acyl chloride. Following our previous studies concerning the Nef reaction (α-addition of acyl chlorides to isocyanides giving acyl imidoyl chlorides),[6] we presumed that a terminal acyl group might alter the acidity of the compound. This would, in turn, allow electrophilic additions under smoother conditions and lead to an overall three-component extension of the Schöllkopf synthesis (Scheme 2).

The first trials with diazonium salts were quite deceiving, since when an equimolar mixture of *p*-chlorobenzylisocyanide and benzoyl chloride was heated in toluene at 60 °C, and then a stoichiometric amount of triethylamine and *p*-nitrophenyl diazonium tetrafluoroborate was added, none of the expected triazole could be isolated. More interestingly, traces of a new oxazole were observed, which just retained the structural elements present in the Nef adduct. We then performed blank assays by heating the Nef adduct with various bases; in all cases, the corresponding 2,5-disubstituted oxazole, **3a**, was isolated (Scheme 3). In the light of the known reversibility of the Nef reaction in the presence of nucleophilic bases,[6a,b] 2,6-lutidine was finally selected and added at the beginning of the Nef reaction to give **3a** in a 60% isolated yield. Its structure was confirmed by an alternative preparation of the same compound from 1-azidoacetophenone and *p*-chlorobenzoyl chloride.[7] The analysis of these results in light of the Schöllkopf reaction shows that the change of base leads to a completely different reaction path. Strong bases afford 4,5-disubstituted oxazoles, whereas 2,6-lutidine gives 2,5-disubstituted regioisomers (Scheme 3).

Various isocyanides **1** and acyl chlorides **2** were treated under these optimized conditions to form oxazoles **3** in moderate to good yields (Table 1). Both aromatic and aliphatic acyl chlorides participated in this new coupling. Considering the isocyanide component, the reaction is compatible with the presence of heteroaromatic rings, such as pyridyl (Table 1, entries 8–10) and furyl (Table 1, entries 11–12). With a pyridyl-substituted isocyanide, the basic nature of the pyridyl allowed the formation of the new oxazole without any additional base, but in a moderate 32% yield. However, the addition of 2,6-lutidine raised the yield to 62%. Allylic isocyanides may also be used in this reaction, though with slightly lower yields (Table 1, entry 13). Unfortunately, aliphatic isocyanides treated with benzoyl chloride (Table 1, entry 15) failed to give any oxazole using 2,6-lutidine or stronger bases, such as DBU.

We were rather puzzled by the possible mechanism of this reaction. A careful look at the literature revealed that a similar synthesis of an oxazole ring was observed after basic treatment of a Nef adduct derived from isocyanoacetate (Scheme 4).[8] However, the regioselectivity of the process is opposite to the one we observed. In our case, the mechanism might be related to the oxazole formations reported by Zhu *et al.*[9]

Nitrilium ylides are the most likely intermediates in this oxazole formation from Nef adducts. Indeed [3 + 2]-cycloadditions have already been observed by the basic treatment of Nef adducts with dipolarophiles.[10] In the case of oxazoles, an electrocyclization of a nitrilium ylide intermediate may be the key step. However, if such a process is easy to imagine, with the formation of oxazoles from isocyanoacetates, the direct cyclization of nitrilium ylide **A** to **3** is less obvious



Scheme 1 Oxazole formation from isocyanides.

Laboratoire Chimie et Procédés, UMR 7652, Ecole Nationale Supérieure des Techniques Avancées, 32 Bd Victor, 75015 Paris, France. E-mail: laurent.elkaim@ensta.fr, laurence.grimaud@ensta.fr; Fax: +33 145528322; Tel: +33 145525537

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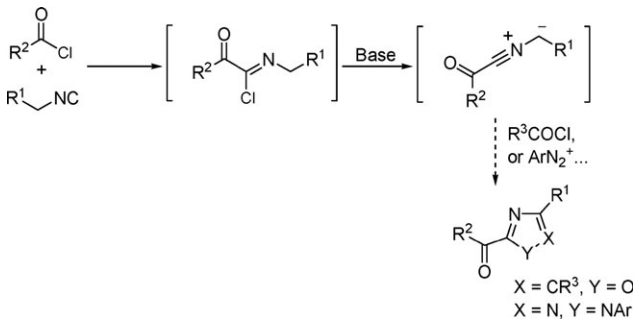
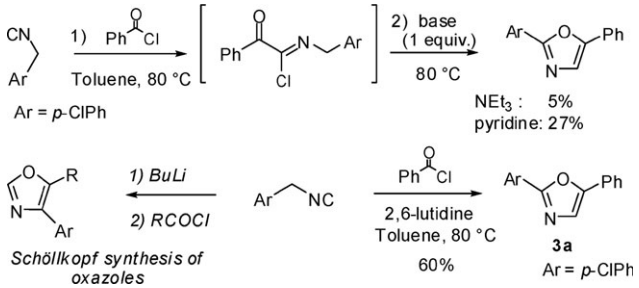
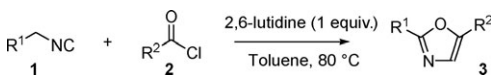


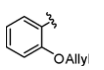
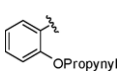
Scheme 2 Three-component extension of the Schöllkopf synthesis.

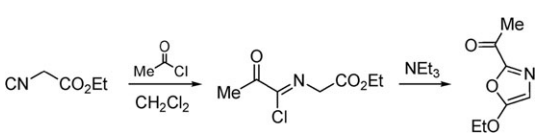


Scheme 3 Nef *vs.* Schöllkopf access to oxazoles from benzylisocyanides.

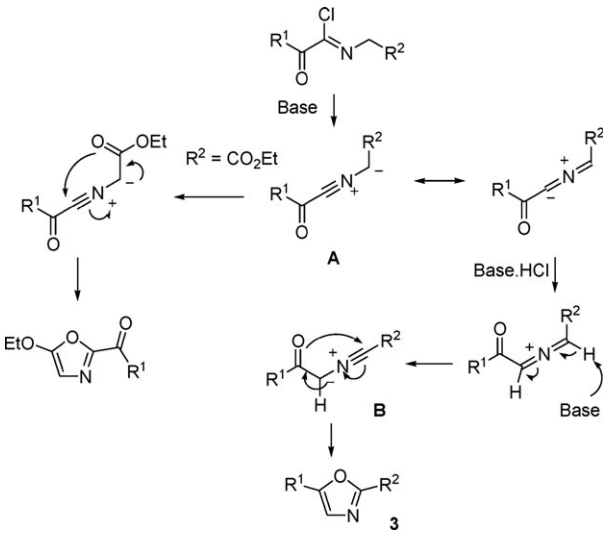
Table 1 Oxazoles from acyl chlorides and isocyanides



Entry	R^1	R^2	Product	Yield (%)
1	*p*-ClPh	*p*-FPh	**3b**	79
2	*p*-ClPh	*n*-Pr	**3c**	59
3	*p*-ClPh	Cyclopropyl	**3d**	81
4	*p*-ClPh	*i*-Pr	**3e**	73
5	*p*-ClPh		**3f**	58
6	*p*-FPh	Ph	**3g**	57
7	*p*-FPh	*i*-Pr	**3h**	58
8	3-Pyridyl	*i*-Pr	**3i**	62
9	3-Pyridyl	Ph	**3j**	50
10	3-Pyridyl	*p*-FPh	**3k**	56
11	2-Furyl	*i*-Pr	**3l**	51
12	2-Furyl	*p*-FPh	**3m**	40
13	1-Styryl	*i*-Pr	**3n**	48
14	*p*-ClPh		**3o**	49
15	$MeO(CH_2)_2$	Ph	—	—



Scheme 4 Oxazole formation from isocyanoacetates.



Scheme 5 Mechanism of oxazole formation from the Nef adduct.

(Scheme 5). A reasonable path would involve the conversion of nitrilium ylide **A** into intermediate **B** by a protonation–deprotonation sequence. The final cyclization of new nitrilium ylide **B** into oxazole **3** can then be readily considered.

First disclosed by the groups of Van Leusen and Schöllkopf,[4,5] the synthesis of oxazole derivatives using isocyanides as starting materials was encouraged by a renewed interest in isocyanides and multi-component reactions. In all of those reactions, the oxazoline ring was usually obtained by the intramolecular addition of an oxygen atom onto the isocyanide terminal carbon. Our studies on the interaction of isocyanides with acyl chlorides have led us to disclose an alternative cyclization mode of isocyanides into oxazoles.‡ We are currently exploring analogous reactions using other electrophilic trapping agents instead of acyl chlorides.

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Notes and references

‡ A typical procedure: A solution of 1.0 mmol (1.0 equiv.) of isocyanide, 1.0 mmol (1.0 equiv.) of acyl chloride and 1.0 mmol (1.0 equiv., 115 μL) of 2,6-lutidine in 2 mL of toluene was warmed at 80 °C with stirring under an atmosphere of argon overnight. The solution was then washed with water and citric acid. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were concentrated *in vacuo* and purified by flash column chromatography silica gel using a mixture of petroleum ether/diethyl ether as the eluent. 2-(4-Chlorophenyl)-5-propyl oxazole (**3c**): yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.96 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 6.87 (s, 1H), 2.72 (t, 2H, J = 7.6 Hz), 1.75 (sext., 2H, J = 7.6 Hz) and 1.04 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 160.1, 153.5, 136.2, 129.4, 127.7, 126.7, 124.4, 28.0, 21.0 and 13.6. IR (thin film): ν 1014, 1092, 1123, 1406, 1483, 1545 and 1609 cm^{-1}; HRMS calc. for $C_{12}H_{12}ClNO$: 221.0607, found: 221.0616.

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