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One-pot synthesis of oxazoles using isocyanide surrogates

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ABSTRACT

We wish to present herein a simple one-pot synthesis of 2,5-disubstituted oxazoles, starting from benzyl halides and acyl chlorides. The in situ formation of isocyanides, followed by the addition of an acyl chloride in the presence of a base leads to the desired oxazoles in good yields.

Green chemistry, with its principles of step and atom economy, has grown into being a major theme in organic research in the 21st century. It often involves the association of several transformations in a single reaction vessel, without requiring work-up and isolation of intermediates.[1] In our search for operationally simple, resource- and cost-effective processes, we have been investigating isonitrile-based multicomponent reactions (IMCRs) using in situ-generated isocyanides. Their classical syntheses (dehydration of *N*-formamides[2] and carbylamine reaction[3]), combined with their foul odor, are indeed strong deterrents for a wider use of isocyanide-based reactions.

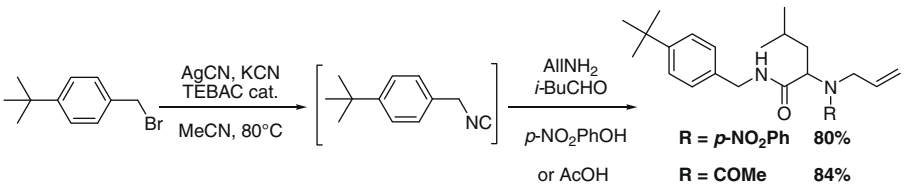
Inspired by the previous works of Lieke[4] and Songstad,[5] we recently published an efficient and time-saving method that allowed two different subsequent Ugi-type four-component couplings, using an activated benzyl or allyl bromide in the presence of silver and potassium cyanide[6] (Scheme 1).

In order to further extend the scope of this process, we are currently exploring other reactions involving isocyanides. Having recently reported a new synthesis of 2,5-disubstituted oxazoles starting from an acyl chloride and a benzylic isocyanide (Scheme 2),[7] we now wish to disclose a one-pot two-step sequence that provides such oxazoles thanks to in situ-made isocyanides.

In the first step, isocyanides are readily obtained by heating overnight at 80 °C stoichiometric amounts of bromide derivative, silver cyanide, and potassium cyanide in acetonitrile with a catalytic amount of triethyl benzyl ammonium chloride (TEBAC).

The Nef-isocyanide coupling between the acyl chloride and the isocyanide affords a nitrilium ylide intermediate which cyclizes upon a proton exchange with a weak base to give the corresponding 2,5-disubstituted oxazole.[7]

Obviously, the 'free' remaining equivalent of cyanide ions in the medium might trigger a potential acyl cyanide formation upon acyl



Scheme 1. One-pot Ugi and Ugi-Smiles processes.

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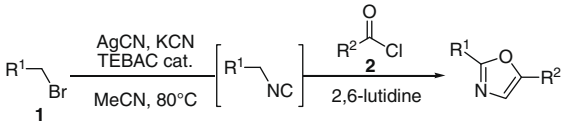
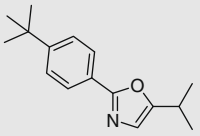
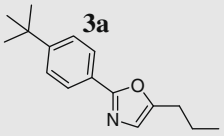
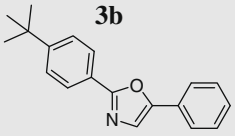
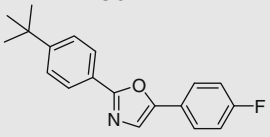
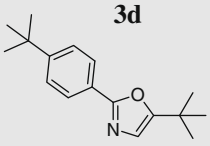
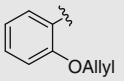
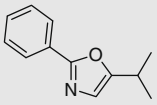
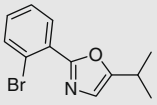
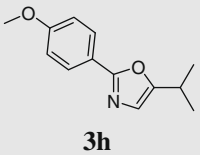
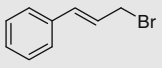
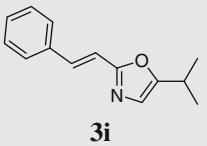
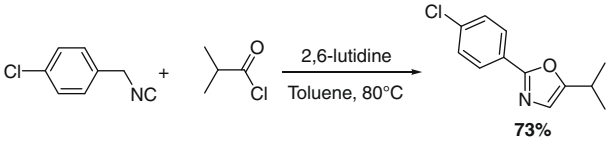
Table 1
Two-step sequence yielding 2,5-disubstituted oxazoles



Entry	Bromide derivative	R^2	Product	Yield (%)
1	*p*-*t*BuBnBr **1a**	*i*Bu **2a**	 **3a**	70
2	**1a**	Bu **2b**	 **3b**	40
3	**1a**	Ph **2c**	 **3c**	41
4	**1a**	*p*-FPh **2d**	 **3d**	34
5	**1a**	*t*Bu **2e**	 **3e**	35
6	**1a**	 **2f**	–	–
7	BnBr **1b**	**2a**	 **3f**	50
8	*o*-BrBnBr **1c**	**2a**	 **3g**	40
9	*p*-OMeBnBr **1d**	**2a**	 **3h**	32
10	 **1e**	**2a**	 **3i**	33
11	AllBr **1f**	**2a**	–	–



Scheme 2. Synthesis of 2,5-disubstituted oxazoles.

chloride addition. Furthermore, as the oxazole synthesis was first developed in toluene, there was no guarantee that the coupling would take place in acetonitrile.

However, we were delighted to observe the sole formation of oxazoles (Table 1) when introducing equivalent amounts of acyl chloride and base in the isocyanide mixture heated at 80 °C overnight. This procedure gave satisfying results: various benzyl bromides behaved similarly as potential isocyanides to provide these heterocycles.[8] The reaction proceeded smoothly in fair yields, ranging from 32% to 70%. However, the functionalized acyl chloride **2f** that had previously afforded the oxazole in good yields in the previous study did not react under these modified conditions.

Although allyl isocyanide was formed, it failed to perform such a coupling. However, cinnamyl bromide turned out to be a moderate reactant: upon reaction with isobutyryl chloride, it provided the corresponding oxazole **3i** with a 33% yield. Considering the earlier recorded 48% yield obtained in the one-step reaction from isolated cinnamyl isocyanide, this two-step procedure favorably competes with the classical isocyanide syntheses.

As a conclusion, we have settled a straightforward oxazole synthesis, which usefully complements the Schöllkopf oxazole formation,[9] affording 2,5-disubstituted oxazoles instead of the classical 3,4-disubstituted isomers.[10] This reaction involves commercially available reactants: the reasonably priced silver cyanide, and bromide derivatives. The latter can de facto be seen as isocyanide surrogates, later reacting with an acyl chloride in the presence of a base to afford the awaited oxazoles. No handling of isocyanide is required, therefore enhancing the interest in isocyanide chemistry while removing its less enticing aspects.

Acknowledgments

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References and notes

1. Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438–440.
2. Ugi, I.; Meyr, R. *Chem. Ber.* **1960**, *93*, 239–248; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupper, H.; Offermann, K. *Angew. Chem.* **1965**, *77*, 492–504; Angew. Chem., Int. Ed. Engl. **1965**, *4*, 472–484; Ugi, I.; Meyr, R.; Lipinski, M.; Bodensheim, F.; Rosendahl, F. *Org. Synth.* **1973**, *coll vol V*, 300–302.
3. Hoffmann, A. W. *Ann. Chem. Pharm.* **1867**, *144*, 114–120; Weber, W. P.; Gokel, G. W.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 530–531; Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth.* **1988**, *coll vol VI*, 232–235.
4. Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316.
5. Songstad, J.; Stangeland, L. J.; Austad, T. *Acta Chem. Scand.* **1970**, *24*, 355–356; Engemyr, L. B.; Martinsen, A.; Songstad, J. *Acta Chem. Scand. Ser. A* **1974**, *28*, 255–266.
6. El Kaim, L.; Grimaud, L.; Schiltz, A. *Synlett* **2009**, 1401–1404; El Kaim, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.*, 2009, doi:10.1039/b908541f.
7. Dos Santos, A.; El Kaim, L.; Grimaud, L.; Ronsseray, C. *Chem. Commun.* **2009**, 3907–3909.
8. *Typical procedure for* **3f**: To a solution of 120 μL of benzyl bromide (1.0 mmol, 1.0 equiv) in 0.5 mL of acetonitrile were added 134 mg of silver cyanide (1.0 mmol, 1.0 equiv), 65 mg of potassium cyanide (1.0 mmol, 1.0 equiv), and 46 mg of TEBAC (0.2 mmol, 20 mol %). The mixture was then stirred at 80 °C overnight. The formation of the isocyanide could be checked via ^{1}H NMR analysis of an aliquot. 140 μL of isobutyryl chloride (1.3 mmol, 1.3 equiv), and 116 μL of 2,6-lutidine (1.0 mmol, 1.0 equiv) were then added to the mixture,

which was stirred at 80 °C overnight. After checking the completion of the reaction via TLC, the reaction is quenched with the addition of water and diluted with dichloromethane. The organic phase is then washed several times with water acidified with citric acid, dried over $MgSO_4$ and concentrated in vacuo. A flash column chromatography on silica gel (diethyl ether/petroleum ether 90/10) affords the desired product **3f** as a colorless oil (94 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.1, 1.8 Hz, 2H), 7.49–7.43 (m, 3H), 6.83 (d, J = 1.0 Hz, 1H), 3.07 (sept d, J = 6.8, 1.0 Hz, 1H), 1.35 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.9, 158.8, 130.3, 129.1, 128.3, 126.4, 122.2, 26.5, 21.2. IR (thin film) 2970, 1699, 1594, 1551, 1487, 1148 cm^{-1}. HRMS calcd for $C_{12}H_{13}NO$ 187.0997, found 187.0998.

9. Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533–546.
10. For some recent oxazole synthesis from isocyanides: Wang, Q.; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6825–6827; Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485–2488; Elders, N.; Ruijter, E.; Kanter, F.; Groen, M.; Orru, R. *Chem. Eur. J.* **2008**, *14*, 4961–4973; Janvier, P.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291–4294.