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Amidinyl radicals: new and useful intermediates for the synthesis of imidazolines and imidazoles

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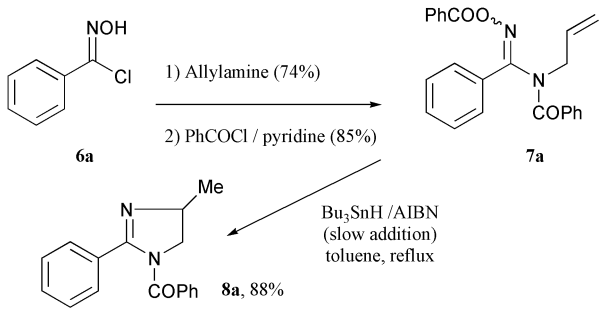
Amidinyl radicals are readily generated from amidoxime benzoates by treatment with a stannane–diazo initiator or with Ni–AcOH and captured by an internal olefin to give the corresponding imidazoline.

As part of our work on the generation and capture of nitrogen centred radicals,[1] we had briefly examined the possibility of accessing 1,2-diamines through the internal capture of ureidyl radicals such as **3** (Scheme 1). Unfortunately, our initial efforts were frustrated by a disappointingly low yield in the cyclisation step, as shown by the inefficient conversion of **1** into imidazolinone **2**.[2] This is presumably caused by a slow rotation around the amide-like bond so that the equilibrium leading to the radical intermediate with the correct geometry for cyclisation cannot compete with premature hydrogen abstraction from the stannane.

This problem is well known in the analogous and much better documented case of amides.[3] Amidinyl radicals **4**, in contrast, would not be expected to suffer from such limitations and appeared from the outset to be ideally suited for our purposes. The reactivity of these intermediates, as far as we could tell, had not hitherto been studied, despite their obvious synthetic potential.

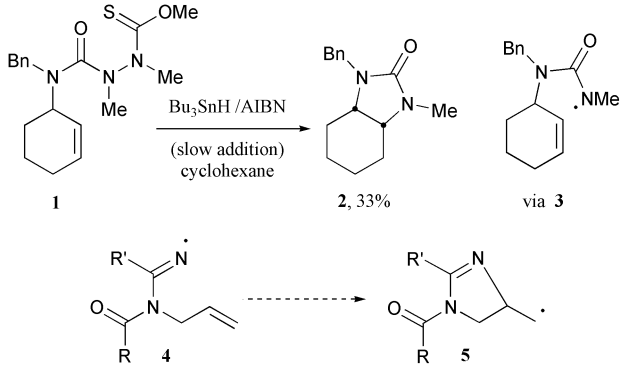
Oxime benzoates were found in the past to be convenient precursors for iminyl radicals[4] and, in principle, the analogous amidoxime benzoates could act as substrates for generating the corresponding amidinyl radicals. The amidoxime benzoates are easily assembled by reacting an allylic amine[5] with an oximinoyl chloride, itself obtained by chlorination of an aldoxime, followed by benzoylation. This sequence is illustrated in Scheme 2 by the synthesis of **7a**, obtained as essentially one geometrical isomer; but since this had no influence on the subsequent step no attempt was made to establish which of the two isomers it was. We were indeed pleased to find that slow addition of a solution of tri-*n*-butylstannane and AIBN in toluene to a refluxing solution of amidoxime benzoate **7a** in the same solvent indeed resulted in the smooth formation of the corresponding imidazoline **8a** (88%).



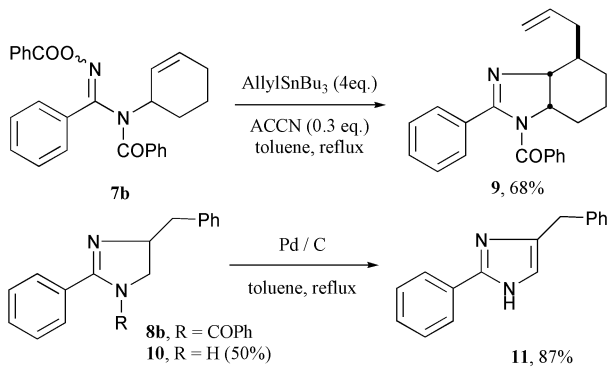
Scheme 2 Synthesis of an imidazoline.

This reaction was extended to various amidoxime benzoates, as shown by the results compiled in Table 1. Bicyclic and spiro imidazolines could be readily prepared as well as derivatives containing quaternary centres. The synthesis of the glucal derived imidazoline is especially noteworthy. Furthermore, we later found that slow addition of the stannane was not necessary: mere heating of the amidoxime benzoate (0.5 mmol), tri-*n*-butyltin hydride, and 0.2 equiv. of 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in refluxing toluene (5 ml) was sufficient to bring about the desired transformation in good yield.† By analogy with the case of iminyls,[6] the reduction of the amidinyl radicals by the stannane appears to be sufficiently slow to allow the cyclisation to proceed unimpeded by premature reduction even under relatively concentrated conditions. This represents a notable simplification in the experimental procedure.

The use of allyl tri-*n*-butylstannane in the case of substrate **7b** resulted in the clean formation of allyl imidazoline **9** (Scheme 3). As expected allylation occurs from the least hindered *exo* face to give the isomer shown. In addition to being precursors of 1,2-diamines by acid hydrolysis,[7] imidazolines can be oxidised to imidazoles.[8] The latter transformation is illustrated by the synthesis of imidazole **11** by saponification of **8b** with methanolic sodium hydroxide, followed by heating the resulting imidazoline **10** in toluene under air in the presence of palladium over charcoal.



Scheme 1 Cyclisation of ureidyl and amidinyl radicals.



Scheme 3 Cyclisative allylation and synthesis of imidazole.

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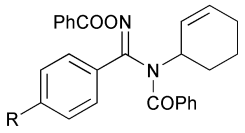
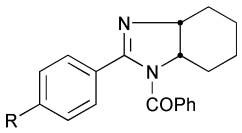
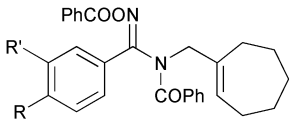
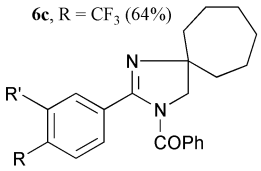
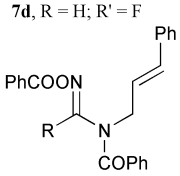
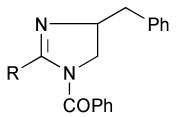
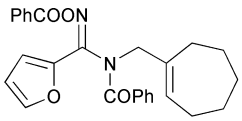
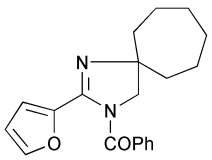
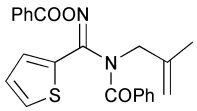
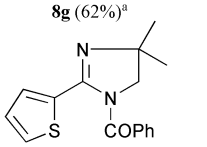
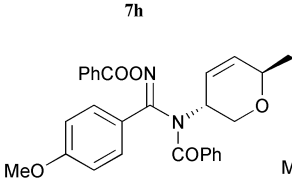
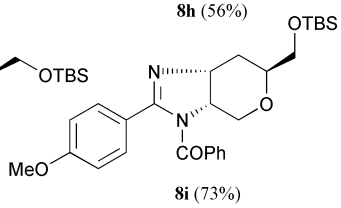
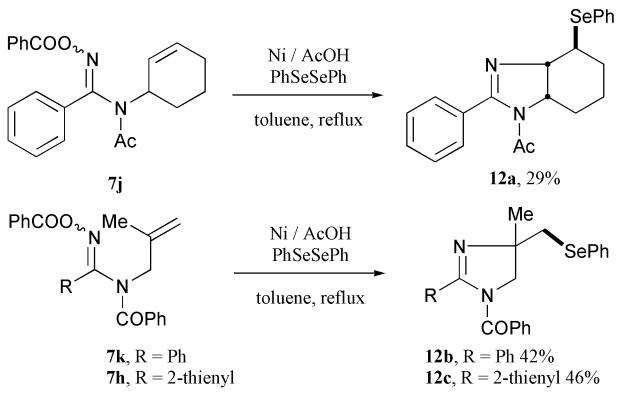
Table 1 Synthesis of imidazolines **8** from amidoxime benzoates **7**

Amidoxime benzoates **7**	Imidazolines **8**
	
2b, R = H **2c**, R = OMe **2d**, R = CF_3	**6b**, R = H (88%)[a] **6c**, R = OMe (70%) **6c**, R = CF_3 (64%)
	
7b, R = R' = H **7c**, R = OMe; R' = H **7d**, R = H; R' = F	**8b**, R = R' = H (92%)[a] **8c**, R = OMe; R' = H (82%) **8d**, R = H; R' = F (82%)[a]
	
7e, R = Ph **7f**, R = Et	**7e**, R = Ph (88%) **8f**, R = Et (50%)
	
7g	**8g** (62%)[a]
	
7h	**8h** (56%)
	
7i	**8i** (73%)

[a] Yield obtained by simple mixing of reagents (see text).

We have briefly examined the possibility of generating and capturing the amidinyl radical by electron transfer from metallic nickel to the amidoxime ester. We had found previously that this method was useful for producing iminyl radicals from oxime esters.[9] Indeed, heating a mixture of amidoxime benzoate **7j**, nickel powder, and diphenyl diselenide in toluene and acetic acid resulted in the formation of selenide **12a** but in only poor yield (29%; Scheme 4). Somewhat better yields were observed starting from derivatives **7k** and **7h**. Despite the modest, but as yet unoptimised yields, this approach has the advantage of avoiding tin-containing reagents and allowing the synthesis of selenides.

In summary, these preliminary results demonstrate the potential of amidinyl radicals for the synthesis of imidazolines and imidazoles. The precursors are readily available and the radical cyclisation can be easily incorporated into various tandem sequences, thus opening a straightforward access to a variety of complex structures.



Scheme 4 Cyclisative selenylation.

Notes and references

† Typical experimental procedure:

Synthesis of amidoxime benzoates **7**: to a solution of aldehyde (20 mmol) in methanol (20 mL) were added hydroxylamine hydrochloride (22 mmol) and sodium acetate (24 mmol). After 20 min, the mixture was diluted with water and extracted with ether. The organic layer was dried and concentrated. The residue was dissolved in DMF (10 mL) and NCS (20 mmol) was added portion-wise. Once the reaction was complete (TLC), the solution was diluted with water and extracted with ether. The organic layer was dried, concentrated, and the crude oximinoyl chloride (**CAUTION:** oximinoyl chlorides can be harmful and allergenic) added to a solution of the allylic amine (25 to 50 mmol) in dry ether (50 mL). After 12 hours, the mixture was diluted with water and extracted with ether. The organic layer was dried and concentrated. The residue was dissolved in pyridine (15 mL), and benzoyl chloride (50 mmol) was added dropwise at room temperature. After 12 to 24 hours, the solution was diluted with water, extracted with ether, and the organic layer washed twice with 1 M citric acid, water, saturated aqueous $NaHCO_3$, water, saturated aqueous $CuSO_4$ and brine, then dried and concentrated. Filtration of the oily residue over a silica pad removes the last traces of amine and other polar impurities from the amidoxime benzoate **7** which can then be recrystallised from ether. The overall yield in the sequence was generally greater than 50%.

Radical cyclisation: to a solution of amidoxime benzoate **7** (0.5 mmol) in toluene (5 mL), degassed by refluxing for a few minutes under argon, were added Bu_3SnH (0.6 mmol) and ACCN (30 mg). After 30 minutes at reflux, the mixture was allowed to cool to room temperature and was concentrated. The residue was purified by chromatography on silica gel (petroleum ether, then ethyl acetate–petroleum ether 2 : 8) to give compound **8**, which could generally be recrystallised from ether.

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