

Direct Synthesis of Polysubstituted Aluminoisoxazoles and Pyrazoles by a Metalative Cyclization

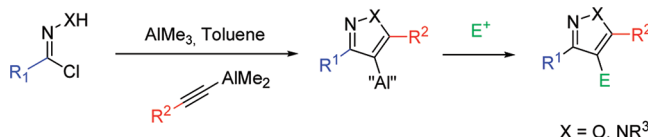
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ABSTRACT



Alumino-heteroles are obtained from simple precursors in a fully chemo- and regioselective manner by a metalative cyclization. The carbon–aluminum bond is still able to react further with several electrophiles, without the need of transmetalation. This synthetic route provides a novel entry to heterocyclic organoaluminum reagents as well as a straightforward access to 3,4,5-trisubstituted isoxazoles and 1,3,4,5-tetrasubstituted pyrazoles.

The preparation of main-group aryl and heteroaryl organometallics is a very active field, as these reagents are key intermediates in diversity-oriented elaboration of compounds for pharmaceutical and material science applications.¹ In this context, the preparation of aryl- or heterocyclic organoaluminum reagents has gained a renewed interest, due to their potential broad functional tolerance² and the low cost and toxicity of alanes.³

A conventional preparative method for aromatic organoaluminum compounds has been the transmetalation of the corresponding lithium or magnesium derivatives with

various aluminum(III) sources,⁴ or in some cases through aluminum–tin or boron exchange reactions.⁵ However, the transmetalation pathway, generally conducted at low temperature from reactive organolithium reagents,⁶ generates salts as side products. These salts have been reported to strongly affect the reactivity⁷ of the final organoaluminum reagent and the enantioselectivity of asymmetric processes.⁸ This procedure is very often conducted in ethereal solvents, known to strongly decrease the Lewis acidity of organoaluminum reagents and, therefore, to affect their reactivity. Finally, the potential functional group tolerance of the carbon–aluminum bond cannot be exploited if

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(3) Although organoaluminum reagents are usually regarded as hazardous reagents, their pyrophoric character is mainly a problem with low-molecular weight reagents, such as trimethylaluminum, and is drastically reduced when working with diluted solutions in hydrocarbons. The nonpyrophoric limits for trimethylaluminum are 11 wt% in hexane and 14 wt% in heptane: (a) Suzuki, K.; Nagasawa, T. In *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd: Chichester, 1995; Vol. 7, p 5186. Thus, a commercially available 2 M solution of trimethylaluminum in heptane can be handled like a commercially available MeLi or BuLi solution. This is confirmed by comparable safety data sheet hazards identification according to EC regulations between these reagents. In this work, we only used commercially available 2 M solutions of trimethylaluminum. For a discussion on this problem, see also: Von Zezschwitz, P. *Synthesis* **2008**, 1809.

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organoaluminum reagents are prepared from the corresponding lithiated or magnesiated derivatives.⁹

More recently, several alternative procedures, based on directed metalation¹⁰ or oxidative insertion,² have been reported, leading to functionalized aromatic organoaluminum compounds. However, in most cases, these organo-metallic reagents must be transmetalated before further reaction. New alternative routes to aluminated heterocycles are therefore desirable.

In our ongoing work in the field of organoaluminum chemistry,¹¹ we have reported the preparation of functional aluminotriazoles by a copper catalyzed cycloaddition of organic azides and mixed aluminum acetylides.¹² Herein, we report that aluminated heterocycles can be prepared by a tandem addition/intramolecular 5-endo-dig metalative cyclization mechanism (Figure 1). This kind of cyclization is well preceded for transition-metal-catalyzed synthesis of various heterocycles,¹³ and it has been shown that a stoichiometric amount of metalated precursor can lead to metalated benzoheterocycles in an efficient manner.¹⁴ However, despite these examples, such a pathway has never been used to prepare aluminated heterocycles.

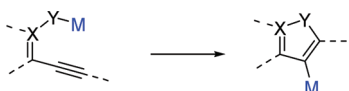
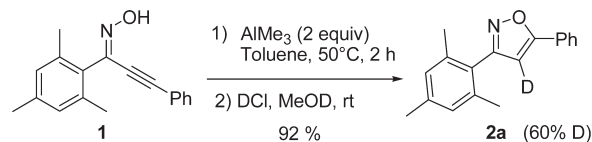


Figure 1. General principle of metalated heterocycles synthesis by a metalative cyclization process.

We first turned our attention to aluminated isoxazoles synthesis. Isoxazole is indeed a privileged structure encountered in numerous compounds with biological activities,

natural products, and functional materials.¹⁵ Furthermore, access to these structures from alkynyloxime using catalytic¹⁶ or stoichiometric electrophilic activation¹⁷ is well documented.

Scheme 1. Metalative Cyclization of Oxime 1



Cyclization product **2a** was indeed obtained in 92% yield, starting from compound **1** in the presence of 2 equiv of trimethylaluminum (Scheme 1). However, only partial (60%) deuterium incorporation was observed. This modest deuterium incorporation can be explained by a competitive *in situ* protonation of the aluminated intermediate.¹⁸ In order to avoid this troublesome side reaction, we decided to generate the metalated precursor directly from nitrile oxide **3**. Although nitrile oxides are not considered as electrophiles, complexation to aluminum reagents could increase their electrophilicity and decrease their dipole reactivity, as already noticed by Kanemasa and co-workers.¹⁹ To our delight, 93% deuterated isoxazole **2a** was obtained with 2 equiv of dimethyl-phenylalkynylaluminum²⁰ and mesitylene carbonitrile oxide, after deuterolysis of the reaction mixture (Table 1, entry 1). The use of only 1 equiv of aluminum acetylide led to the formation of alkynyl oxime **1** as a major reaction product (entry 2), showing that external electrophilic assistance is required to trigger the cyclization. Thus, addition of 1 equiv of AlMe_3 after initial reaction between nitrile oxide and aluminum acetylide resulted in the clean formation of compound **2a** in 76% isolated yield (Table 1, entry 3). Interestingly, even a substoichiometric amount of AlMe_3 can assist the reaction, although 20% are needed to achieve a correct conversion (entry 4).

All these experiments support a tandem addition/intramolecular 5-endo-dig metalative cyclization mechanism (Scheme 2).²¹ Although the role of aluminum π -acidity is well-known in carbo- and hydroalumination reactions, and several examples have been reported showing that

(9) The good functional group tolerance of trimethylaluminum is for instance used in many copper-catalyzed asymmetric transformations, or in a trimethylaluminum-assisted transformations, where AlMe_3 acts as a nonreactive methyl donor and/or Lewis acid.

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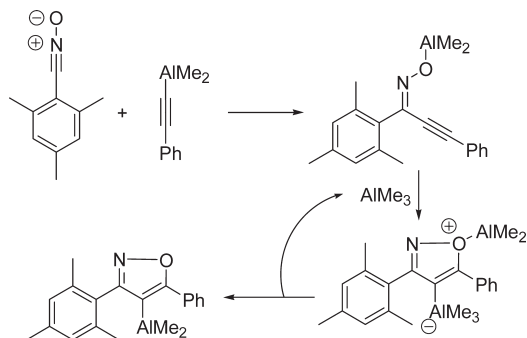
(21) NMR monitoring of the reaction with mesitylene carbonitrile oxide clearly demonstrated the absence of any protonated species before quenching with deuterium chloride. We also have checked that no aluminated protonated isoxazole can occur under the reaction conditions. The isolation of intermediate **1** rules out a concerted mechanism involving a transient metalacycle, as proposed for copper-catalyzed synthesis of isoxazoles: Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

Table 1. Optimization of the Reaction Conditions

entry	alane (equiv)	additive (equiv)	<i>t</i> (h)	<i>t</i> (°C)	2a/1	yield (%) ^a
1	2	–	4	20	1/0	63
2	1	–	4	20	2/8	– ^b
3	1	AlMe ₃ (1)	1	50	1/0	76
4	1	AlMe ₃ (0.2)	4	50	1/0	68
5	1	AlMe ₃ (0.1)	4	50	1/1	– ^b

^a Isolated yield. ^b >99% conversion. Yield not determined.

aluminum derivatives can trigger a *trans* addition on a triple bond,²² this intramolecular *trans*-hydroxyalumination is, to the best of our knowledge, unprecedented.

Scheme 2. Proposed Mechanistic Pathway

Optimized experimental conditions were then applied to a variety of dimethylaluminum alkynides bearing aromatic, alkyl, chloroalkyl, and alkenyl groups (Table 2). In all the cases, the 3,5-disubstituted 4-metallated isoxazoles were obtained as unique regioisomers, with more than 94% deuterium incorporation at the mechanistically expected 4-position after deuterolysis.

Variation of the nitrile oxide part was then investigated. As unhindered nitrile oxides are notoriously unstable,²³ the formation of aluminated isoxazoles was attempted starting from aromatic (Table 3, entries 1–4) or aliphatic (Table 3, entry 5) hydroximoyl chlorides. Best results were obtained using 1 equiv of trimethylaluminum, followed by 1 equiv of mixed acetylides, leading to the clean formation

Table 2. Scope of the Reaction: Alkyne

entry	R	AlMe ₃ (equiv)	<i>t</i> (h)	compound	yield (%) ^a
1	Ph	1	1	2a	76
2	Ph	0.2	4	2a	68
3	nPr	1	1.5	2b	69
4	nPr	0.2	4	2b	64
5	Cl(CH ₂) ₃	1	1.5	2c	73
6	Cl(CH ₂) ₃	0.2	4	2c	61
7		1	1.5	2d	71
8		0.2	4	2d	60

^a Isolated yield.

of several metallated isoxazoles. Interestingly, not only aromatic but also aliphatic substituted isoxazoles can be obtained in a fully regioselective manner (Table 3, entry 5).

Table 3. Scope of the Reaction: Oxime

entry	R	R'	compd	yield (%) ^a
1	4-Cl-Ph	Ph	4a	70
2	4-Cl-Ph	<i>n</i> Pr	4b	68
3	4-MeO-Ph	<i>n</i> Pr	4c	53
4	Ph	<i>n</i> Pr	4d	73
5	Ph(CH ₂) ₂	<i>n</i> Pr	4e	74

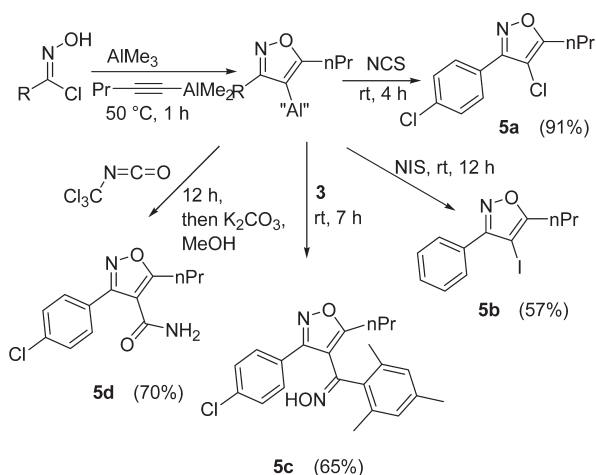
^a Isolated yield.

The reactivity of these new aluminated heterocycles was explored (Scheme 3). Thus, compounds **5a** and **5b** could be obtained by reaction with several *N*-halosuccinimides. Once again, mesitylene carbonitrile oxide proved to be a valuable electrophile, leading to compound **5c** in 65% yield. Introduction of a primary amide functional group could also be realized using a reagent recently proposed by Knochel for the functionalization of organozinc halides.²⁴ Although aryl and/or heteroaryl organoaluminum species are generally transmetalated before further reaction, these last two examples clearly show that a C–C bond formation from aluminated isoxazoles can be performed without the help of any other metal source.

(22) Intermolecular reactions: (a) Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4874. Intramolecular reactions: (b) Asao, N.; Sudo, T.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 7654.

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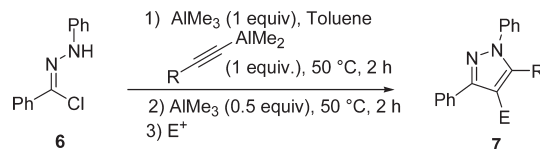
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Scheme 3. Reactivity of Aluminated Isoazoles

Thus, this regioselective one-pot three-component reaction is, to our opinion, a valuable alternative to the direct cycloaddition of nitrile oxides with internal alkynes. This reaction indeed generally suffers from low yield and regioselectivity unless appropriate alkynes, nitrile oxide precursors, and/or subtle kinetically controlled reaction conditions are chosen.²⁵

Finally, extension of this metalative cyclization reaction to the synthesis of aluminated pyrazoles starting from compound **6** was briefly investigated (Table 4). After experimental conditions optimization, we found that an additional amount of 0.5 equiv of trimethylaluminum was necessary to achieve good conversion into the metalated pyrazole. Thus, deuterated pyrazole (91% D) **7a** was obtained in 75% yield as a single regioisomer (Table 4, entry 1). Chlorination using *N*-chlorosuccinimide (NCS) enabled the preparation of chlorinated compounds **7b–e** (Table 4, entries 2–5), showing that aluminated trisubstituted pyrazoles can also be prepared using a metalative cyclization reaction.

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Table 4. Extension to the Synthesis of Aluminated Pyrazoles

entry	R	E ⁺	E	compound	yield (%) ^a
1	nPr	DCl, MeOD	D	7a	75
2	nPr	NCS	Cl	7b	89
3	Cl(CH ₂) ₃	NCS	Cl	7c	84
4	Ph	NCS	Cl	7d	79
5		NCS	Cl	7e	71

^a Isolated yield.

In conclusion, we have developed an access to poly-substituted aluminated heterocycles, based on a metalative cyclization. The regioselectivity of this reaction, combined with the reactivity of the final organoaluminum compounds, enables a rapid and simple access to 3,4,5-trisubstituted isoxazoles with three points of variation introduced in the same operation. We have also shown that this reaction can be extended to the preparation of the corresponding 1,3,5-trisubstituted 4-aluminumpyrazoles. More generally, this synthetic pathway provides an alternative entry to complex heterocyclic organoaluminum reagents, with unexplored reactivity. We expect the present strategy to be applicable to other heterocyclic systems.

Acknowledgment. Financial support from ANR (ANR blanc AluMeth) is acknowledged.

Supporting Information Available. Experimental procedures and characterization of compounds **2a–d**, **4a–e**, **5a–d**, **7a–e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.