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Regiospecific synthesis of α-chloro- and α-fluoro-1,2-diones

Riccardo Surmont [†], Bart De Corte, Norbert De Kimpe [*]

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Gent, Belgium

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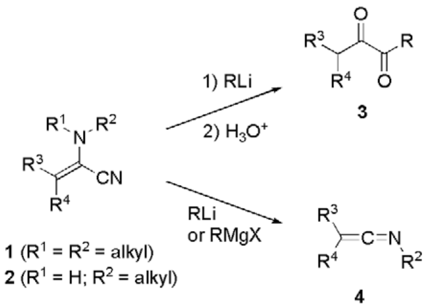
α-Chloro-1,2-diones and α-fluoro-1,2-diones were prepared from the corresponding α-chloroaldimines by a sequence of reactions involving cyanation to α-cyanoenamines, α-halogenation to form α-chloro- or α-fluoroimidoyl cyanides and addition of organolithium reagents across the nitrile moiety, followed by acidic hydrolysis. All steps are straightforward and occur without side reactions finally leading to regiospecifically chlorinated and fluorinated 1,2-diones in good yields.

1,2-Dicarbonyl compounds have found widespread applications in the synthesis of several heterocyclic compounds[1] and many good synthetic approaches for substituted 1,2-diketones have been described.[2] Also halogenated 1,2-diones are useful in pharmaceutical and agrochemical development,[3] although their regiospecific synthesis remained problematic.[4] α-Chloro-1,2-diones have found application in the synthesis of chlorinated (2-amino)-4-acylthiazoles[5] and 3,4-dihydroxythiophenes[6] while α-fluoro-1,2-diones are building blocks for fluorinated (bicyclic) pyrazines,[7] tetrahydrofurans,[8] and imidazoles.[9] The synthesis and reactivity of α-chlorinated and α-brominated imidoyl cyanides have been extensively discussed in previous papers[10,11] but until now α-fluorinated imidoyl cyanides remained unknown. As a part of our investigations in the chemistry of α-fluorinated imines,[12] the synthesis and reactivity of fluorinated imidoyl cyanides, which constitute a promising new class of building blocks for the synthesis of fluorinated azaheterocyclic compounds,[13] were studied. It is known that the addition of organolithium compounds across the nitrile function of N,N-disubstituted α-cyanoenamines **1** leads to adducts[14] which can be hydrolyzed into 1,2-diones **3** (Scheme 1).[15] On the other hand, tautomerizable α-cyanoenamines **2** (R^1 = H; R^2 = alkyl) react with organolithium compounds[16] or Grignard reagents[17] to give deprotonation at nitrogen followed by elimination of cyanide to afford ketenimines **4**. We report now on the selective addition of organolithium compounds across the nitrile function of α-chloroimidoyl cyanides **9** and α-fluoroimidoyl cyanides **10**, thereby not affecting the α-halogen. The resulting halogenated 1,2-diimines **11** and **13** are hydrolyzed toward regiospecifically α-halogenated 1,2-diketones, an interesting class of trifunctional building blocks.

α-Cyanoenamines **8** were prepared from aldehydes **5** via imination to aldimines **6**, α-chlorination to form chloroaldimines **7**,[18] and cyanation resulting in α-cyanoenamines **8**.[19] The obtained compounds **8** were well chlorinated at the α-position in quantitative yield using *N*-chlorosuccinimide in carbon tetrachloride (Scheme 2).[10,11] Fluorination of α-cyanoenamines **8** was performed with *N*-fluorobenzenesulfonimide (NFSI) or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor) as fluorination reagents in acetonitrile at room temperature to afford α-fluoroimidoyl cyanides for the first time.[20] Selectfluor was the reagent of choice because the workup of the reaction mixture was less complicated due to the lower solubility of Selectfluor in organic solvents during extraction, resulting in an easier purification by distil-



Scheme 1. Reaction of organolithium or Grignard reagents with α-cyanoenamines **1** and **2**.

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[*] Corresponding author. Tel.: +32 9 2645951; fax: +32 9 2646243.
E-mail address: norbert.dekimpe@UGent.be (N. De Kimpe).

[†] Aspirant of the Research Foundation—Flanders (FWO—Vlaanderen).

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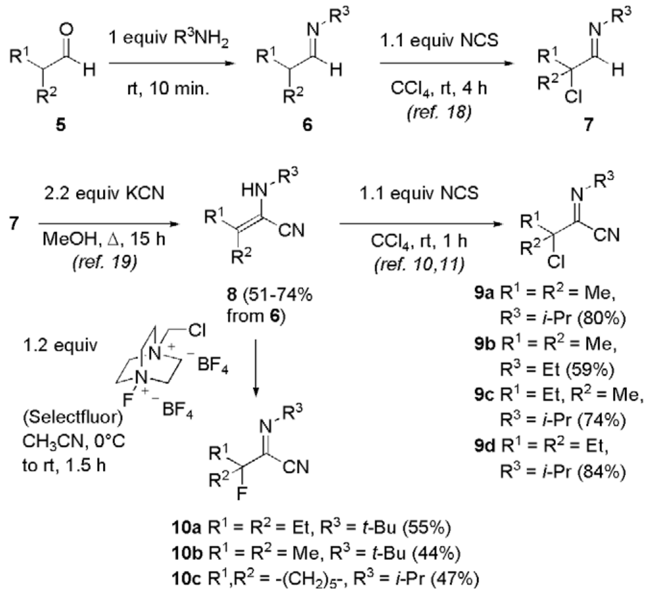
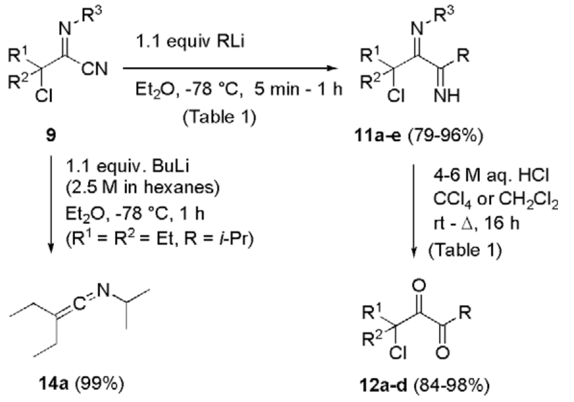


Scheme 2. Synthesis of α-cyanoenamines **8** followed by chlorination or fluorination to α-halogenated imidoyl cyanides **9** and **10**.



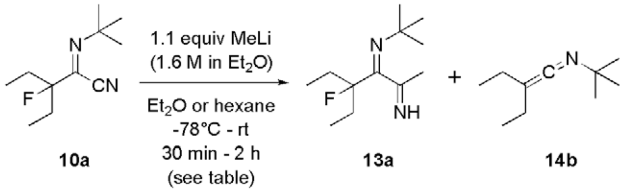
Scheme 3. Reaction of α-chloroimidoyl cyanides **9** with organolithium compounds and subsequent hydrolysis.

lation. Although α-fluoroimidoyl cyanides **10** were obtained in high yields, the purification by distillation resulted in some product decomposition and consequently in lower isolated yields.

Reaction of α-chloroimidoyl cyanides **9** with methyllithium (lithium bromide complex) or phenyllithium (1.8 M in Bu_2O) in diethyl ether at −78 °C afforded α-chloro-1,2-diimines **11** after careful aqueous workup at 0 °C (Scheme 3, Table 1).[21] If the reaction was performed at −20 °C only decomposition products were formed. Surprisingly, the use of butyllithium at −78 °C did not result in the selective addition of butyllithium across the nitrile function but yielded ketenimine **14a**[17] through a chlorine–metal exchange and expulsion of cyanide. A possible explanation for the different behaviors between BuLi and MeLi or PhLi is that BuLi is more basic and reactive than MeLi and PhLi. Consequently BuLi is more prone to induce a lithium halogen exchange. Methyllithium and phenyllithium did not attack the chlorine at −78 °C. The labile 1,2-diimines **11**, bearing an unsubstituted and a substituted nitrogen atom, were fully characterized by spectrometric methods (^{1}H NMR, ^{13}C NMR, IR, GC–MS). In some cases *E*/*Z* isomerism of these imines was observed. Upon hydrolysis with aqueous hydrochloric acid at room temperature in a two-phase system with carbon tetrachloride, these chlorinated 1,2-diimines **11a–d** were almost quantitatively converted into the corresponding α-chloro-1,2-diones **12a–c**.[22] The hydrolysis of phenyldiimine **11e** into 1,2-dione **12d** required more concentrated acid at reflux temperature. The present methodology allows the regiospecific synthesis of 1,2-diones, chlorinated at the α-position. This sequence of reactions leads to an interesting class of trifunctional compounds **12**, the chemistry of which has been only scarcely unraveled.[23]

Analogously, α-fluoroimidoyl cyanide **10a** was treated with 1.1 equiv of methyllithium (1.6 M in Et_2O) (Table 2). However, this reaction at room temperature in diethyl ether only gave traces of diimine **13a**. The major product found was ketenimine **14b**[17] that was formed by a fluorine–metal exchange and expulsion of cyanide (entry 1). Lowering the temperature to 0 °C did favor the attack at the nitrile but did not exclude the lithium fluorine exchange (entry 2). Also the aggregation of organolithium compounds is important for their reactivity, and is highly solvent dependent. In hexane, organolithium compounds are more aggregated and less reactive, compared to etheral solutions. Indeed we observed that MeLi in hexane (at 0 °C) was less reactive for attack at the α-fluorine and

Table 2
Synthesis of 1,2-diimine **13a** from α-fluoroimidoyl cyanide **10a**



Entry	Reaction conditions	10a	13a	14a
1	Et_2O, rt, 30 min	0	6	94[a]
2	Et_2O, 0 °C, 30 min	0	63	37
3	Hexane, 0 °C, 30 min	0	75	25
4	Hexane, −78 °C, 30 min	48	52	0
5	Hexane, −78 °C, 2 h	51	49	0
6	Hexane, −48 °C, 30 min	0	83[b]	0

[a] Not isolated.
[b] Isolated.

Table 1
Synthesis of 1,2-diimines **11** and α-chloro-1,2-diones **12** from α-chloroimidoyl cyanides **9**

R^1	R^2	R^3	R	Reaction conditions **9→11**	**11** Yield[a] (%)	**12** Yield[b] (%)
Me	Me	*i*-Pr	Me	1.1 equiv MeLi.LiBr, Et_2O, −78 °C, 1 h	**11a**: 87	**12a**: 96[b]
Me	Me	Et	Me	1.1 equiv MeLi.LiBr, Et_2O, −78 °C, 5 min	**11b**: 90	**12a**: 94[b]
Et	Me	*i*-Pr	Me	1.1 equiv MeLi.LiBr, Et_2O, −78 °C, 1 h	**11c**: 80	**12b**: 98[b]
Et	Et	*i*-Pr	Me	1.1 equiv MeLi.LiBr, Et_2O, −78 °C, 1 h	**11d**: 79	**12c**: 95[b]
Et	Et	*i*-Pr	Ph	1.1 equiv PhLi (1.8 M in Bu_2O), Et_2O, −78 °C, 1 h	**11e**: 96	**12d**: 84[c]

[a] Compounds **11** were isolated as pure liquids (purity > 95%), which were used as such in the next reaction step.
[b] Compounds **12a–c** were obtained from **11a–d** by hydrolysis with 10 mol equiv 4 M HCl in the presence of CCl_4 during 16 h at room temperature.
[c] Compound **12d** was obtained from **11e** by hydrolysis with 24 mol equiv 6 M HCl in the presence of CH_2Cl_2 during 16 h at reflux.