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Lithium and copper derivatives of munchnone imines

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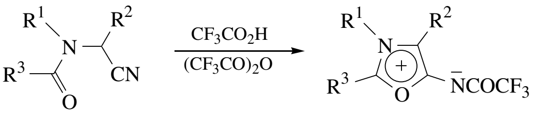
4-Lithium and 4-copper munchnone imines have been obtained, and preparative methods for directly introducing hydroxyalkyl and acyl groups at the 4-position of munchnone imines have been developed.

Munchnone imines (1,3-oxazolium-5-amidines) are typical mesoionic compounds, which are of pharmacological interest. The cyclodehydration of substituted nitriles is the most convenient method for the preparation of munchnone imines.[1]

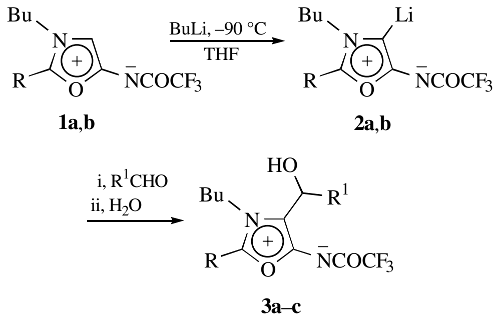


We developed a method for the direct functionalization of munchnone imines using their organometallic derivatives. We found that the treatment of N_6-trifluoroacetyl-2-(4-chlorophenyl)-3-(*n*-butyl)munchnon imine **1a** with *n*-buthyllithium in a tetrahydrofuran solution at –78 °C resulted in the full decomposition of a mesoionic ring. Only a decrease in the temperature to –90 °C and the metalation duration of 5 min followed by the addition of 3-pyridinecarboxaldehyde gave rise to desirable secondary alcohol **3a** in 38% yield. This served as reliable evidence of the formation of 4-lithium derivatives of munchnone imines **2a**.

An increase in the metallation duration to 10–20 min at –90 °C did not enhance the yield of an alcohol but resulted in a decrease in the yield of **3**. These data indicated low stability of 4-lithium derivatives of munchnone imines.

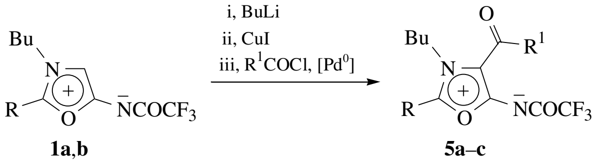
The reaction of 4-lithium derivative **2a** with *p*-chlorobenzaldehyde under the same conditions resulted in alcohol **3b** in 36% yield. The metalation of N_6-trifluoroacetyl-2-phenyl-3-(*n*-butyl)munchnone imine **1b** followed by the addition of 3-pyridinecarboxaldehyde gave alcohol **3c** in 22% yield.

Table 1 Reactivity of 4-lithium organic derivatives of munchnone imines.†



Starting material	R	Product	R¹	Yield (%)	mp/°C
1a	*p*-ClC_6H_4	**3a**	3-Py	38	164–165
1a	*p*-ClC_6H_4	**3b**	*p*-ClC_6H_4	36	161–162
1b	Ph	**3c**	3-Py	22	170–171

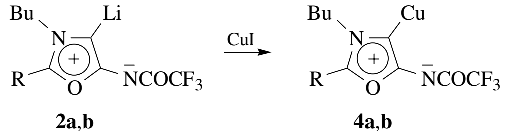
Table 2 Reactivity of 4-copper derivatives of munchnone imines.‡



Starting material	R	Product	R¹	Yield (%)	mp/°C
1a	*p*-ClC_6H_4	**5a**	Ph	38	188–189
1a	*p*-ClC_6H_4	**5b**	*o*-BrC_6H_4	40	169–170
1b	Ph	**5c**	Ph	48	182–183

The low stability of 4-lithium munchnone imines significantly restricts the preparative possibilities of using 4-lithium munchnone imines for the direct functionalization of a munchnone imine ring. It is well known that 4-copper sydnones and sydnone imines have a rather high stability.[2–5] Convenient preparative methods for introducing different substituents at the 4-position of sydnones and sydnone imines *via* palladium-catalysed cross coupling reactions were developed for 4-copper sydnones and sydnone imines. It should be expected that 4-copper munchnone imines are as stable as 4-copper sydnones and sydnone imines.

On adding copper iodide (1 equiv.) to a solution of 4-lithium-2-(4-chlorophenyl)-3-(*n*-butyl)-N_6-trifluoroacetyl munchnone imine **2a** or 4-lithium-2-phenyl-3-(*n*-butyl)-N_6-trifluoroacetyl munchnone imine **2b** at –90 °C, the colour of the reaction mixture deepens, and copper iodide dissolves. This indicates the formation of 4-copper munchnone imines. The decomposition of 4-copper munchnone imines **4a**,**b** did not occur at room temperature.



We studied the possibility of using 4-copper derivatives in palladium-catalysed cross-coupling reactions with some acid chlorides. The results are given in Table 2.

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† *Typical experimental procedure*. A solution of *n*-BuLi in hexane (1.9 mmol) was added to a solution of munchnone imine (1.6 mmol) in 50 ml of absolute THF at –90 °C. The mixture was stirred at –90 °C for 5 min; then, 1.9 mmol of an electrophile were added. After cooling, the mixture was heated to room temperature; 1 ml of water was added; the mixture was diluted with 100 ml of methylene chloride and filtered through a layer of Al_2O_3. The solvent was removed by evaporation, and the residue was chromatographed on SiO_2 (chloroform–diethyl ether, 1:1). The product was crystallised from a methylene chloride–hexane mixture. Satisfactory elemental analyses and ^{1}H NMR data were obtained for all the substances.

‡ *Typical experimental procedure*. A solution of *n*-BuLi in hexane (1.9 mmol) was added to a solution of munchnone imine (1.6 mmol) in 50 ml of absolute THF at –90 °C. The mixture was stirred at –90 °C for 5 min; then, 2.0 mmol of copper(I) iodide were added. The mixture was stirred for 20 min; then, the mixture was heated to room temperature, and 2.1 mmol of an organohalide and 0.1 mmol of (tetrakis-triphenylphosphine)palladium(0) were added. The mixture was stirred for 0.5–2 h until the reaction completed (control by TLC). The reaction mixture was decomposed with water, diluted with 100 ml of methylene chloride and filtered through a layer of Al_2O_3. The solvent was removed by evaporation, and the residue was chromatographed on SiO_2 (chloroform–diethyl ether, 1:1). The product was crystallised from a methylene chloride–hexane mixture. Satisfactory elemental analyses and ^{1}H NMR data were obtained for all the substances.

Thus, 4-lithium and 4-copper munchnone imines were obtained, and their reactivity was investigated for the first time. Preparative methods for the direct introduction of hydroxyalkyl and acyl groups at the 4-position of a munchnone imine ring were developed.

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