Tandem Addition–Bromofunctionalization of γ,δ-Unsaturated Grignard Reagents to Benzonitriles

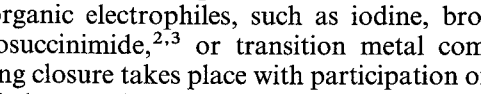
Luc Dechoux,* Louis Jung, Jean-François Stambach

Laboratoire de Chimie Thérapeutique, Université Louis Pasteur, Faculté de Pharmacie, 74 route du Rhin, F-67401 Illkirch, France

Received 11 October 1994

The tandem addition of but-3-enylmagnesium bromide to benzonitriles followed by electrophilic (Br^+) trapping of the intermediate, afforded 2-aryl-5-bromomethyl-3,4-dihydro-2*H*-pyrroles in one step.

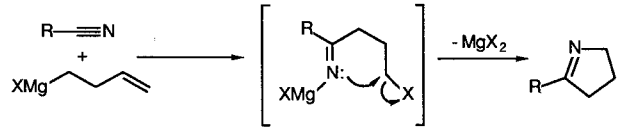
The functionalization of a double bond promoted by an electrophile is one of the most used reactions in organic synthesis. The term "cyclofunctionalization" was introduced by Clive[1] in 1977 to indicate a process where by the addition of an electrophile to an alkene containing an internal nucleophile promotes a cyclization. The carbon of the double bond involved in the ring formation becomes attached to a group specifically chosen to allow further modifications. The vast majority of these cyclizations involves electrophilic addition to an olefin of either organic electrophiles, such as iodine, bromine or *N*-halosuccinimide,[2,3] or transition metal complexes.[2] The ring closure takes place with participation of a number of electron-donating groups, such as –OH, $–NH_2$, –SH, –COOH, etc.[4] It should be pointed out that most of these examples involve the participation of a nucleophile bearing an acidic hydrogen on the heteroatom (Scheme 1).



Scheme 1

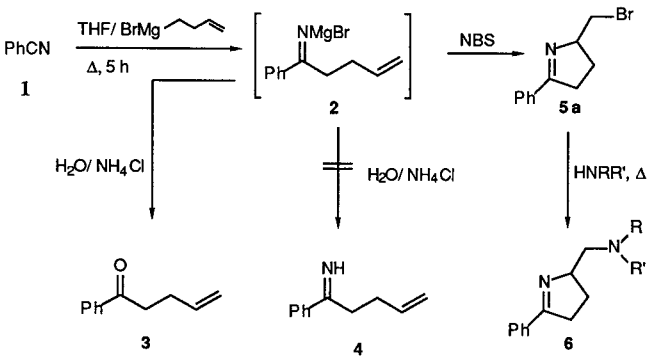
We wish to present herein our approach to 3,4-dihydro-2*H*-pyrrole (1-pyrroline) synthesis by tandem addition of but-3-enylmagnesium bromide to benzonitriles, followed by bromofunctionalization of the γ,δ-unsaturated ketimine salt.

Nucleophilic addition to a cyano group followed by ring closure is a well-documented approach to different heterocycles.[5] Addition by an amino group, an oxygen or a sulfur nucleophile, as well as addition by carbanionic species, followed by cyclization are also well-known reactions. The use of Grignard reagents as precursors for carbon nucleophiles in addition to γ-halonitriles has resulted in the formation of 3,4-dihydro-2*H*-pyrroles[6] (Scheme 2).



Scheme 2

In our current effort to synthesize biologically active 3,4-dihydro-2*H*-pyrrole compounds, we have investigated the possible synthesis of 3,4-dihydro-2*H*-pyrrole **6** by addition of a γ,δ-unsaturated Grignard reagent to benzonitrile **1** followed by bromofunctionalization of the arylketimine **4** (Scheme 3).

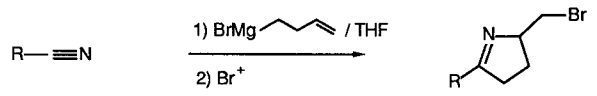


Scheme 3

However, even by careful hydrolysis of the ketimine salt **2**, it has proved impossible to isolate **4**,[7] although we have observed the formation of the hydrolyzed ketone **3**. When the reaction mixture is quenched with *N*-bromosuccinimide (NBS) before hydrolysis, 3,4-dihydro-2*H*-pyrrole **5a** has been obtained in 51% yield (Scheme 3). Only a five-membered ring resulting from a 5-*Exo* cyclization has been observed.

This efficient one-step access to the 5-bromomethyl-2-phenyl-3,4-dihydro-2*H*-pyrrole **(5a)** has prompted us to generalize the methodology to other nitrile substrates. Some representative tandem addition–bromocyclizations are summarized in Table 1.

Table 1

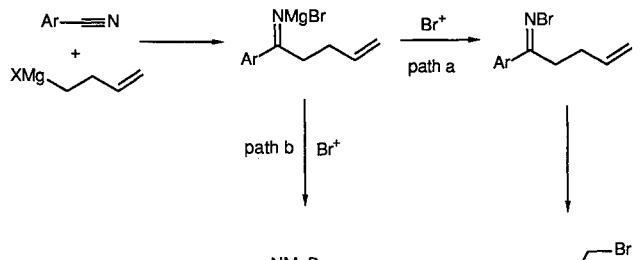


Entry	R	Br^+	Product	Yield (%)[a]
1	Ph	NBS	**5a**	51
2	Ph	Br_2	**5a**	11
3	Ph	NBP	**5a**	39
4	*o*-MeOPh	NBS	**5b**	55
5	*m*-MeOPh	NBS	**5c**	71
6	*p*-MeOPh	NBS	**5d**	63
7	*o*-ClPh	NBS	**5e**	39
8	*m*-ClPh	NBS	**5f**	50
9	*p*-ClPh	NBS	**5g**	56
10	Me	NBS	–	–
11	*tert*-Bu	NBS	–	–

[a] Based on isolated, chromatographically homogeneous material.

Using standard experimental conditions, the methodology only applies to benzonitrile substrates (entries 1–9). When R is an alkyl group (Me, *t*-Bu) no 3,4-dihydro-2*H*-pyrrole structure could be observed by ^{1}H NMR analysis of the crude mixture (entries 10, 11).[8] Using NBS as mild brominating agent gives 3,4-dihydro-2*H*-pyrrole products in average to good yields. No yield improvement could be obtained using *N*-bromophthalimide (NBP) as brominating agent (entry 3). When bromine is used, dramatic yield decrease is observed (entry 2), and in this case we noted a violently exothermic reaction during bromine addition. Due to its slow solubility in tetrahydrofuran, NBS is consumed at a slow rate, allowing the thermal control of the reaction. All 3,4-dihydro-2*H*-pyrroles synthesized are chromatographically stable compounds. No imine–enamine tautomerization was observed.[9]

The reaction most probably proceeds via the π-allyl bromonium species or the three-membered bromonium intermediate (path b, Scheme 4), which is attacked by the internal ketimine salt. Another mechanism could involve a preliminary bromination of the nitrogen atom, followed by migration of the bromonium to the olefin π-bond (path a).[10]



Scheme 4

According to our knowledge this is the first example of ketimine-induced cyclofunctionalization and the first tandem Grignard addition–bromocyclization. The generalization of this tandem Grignard addition to nitriles, followed by intramolecular electrophilic trapping to give ketones, aldehydes, esters, epoxides and isocyanates, is currently being studied.

^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz respectively on a Bruker AC200 spectrometer. IR spectra were recorded on a 8101M FT Shimadzu spectrometer. Mass spectra were recorded on a Sisons Trio 2000 spectrometer. Purifications of products were performed by flash chromatography on silica gel (Merck 60) with mixtures of hexane and EtOAc.

2-Aryl-5-bromomethyl-3,4-dihydro-2*H*-pyrroles; General Procedure: To a solution of but-3-enylmagnesium bromide in THF (2.5 mL of a 2 M solution; 5 mmol) was addded the nitrile (5 mmol). The mixture was refluxed for 5 h, then quenched at 0 °C by addition of NBS (0.94 g, 5.3 mmol) over a period of 1 min. After completion of addition, the reaction was allowed to reach r.t. and stirred for a period of 30 min. Brine (10 mL) was added, and the mixture extracted twice with EtOAc (30 mL). The organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography to give the corresponding 1-pyrroline **5**.

5-Bromomethyl-2-phenyl-3,4-dihydro-2H-pyrrole **(5a)**:
IR (neat): ν = 1615 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.91 (m, 1H, H4), 2.26 (m, 1H, H4'), 3.04 (m, 2H, H3), 3.64 (dd, J = 6.4–10.0 Hz, 1H, CHBr), 3.80 (dd, J = 4–10.0 Hz, 1H, CH'Br), 4.60 (m, 1H, H5), 7.42 (m, 3H, Harom.), 7.85 (dd, J = 1.6–3.0 Hz, 2H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 28.1, 36.6, 38.8, 74.1, 128.6, 129.2, 131.5, 135.1, 174.8.
MS (EI): *m/z* (%) = 239 (19, M + 2$^+$), 237 (19, M$^+$), 144 (100), 130 (11), 85 (21), 83 (34).

5-Bromomethyl-2-(2-methoxyphenyl)-3,4-dihydro-2H-pyrrole **(5b)**:
IR (neat): ν = 1605 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.6 (m, 1H, H4), 2.21 (m, 1H, H4'), 3.08 (m, 2H, H3), 3.62 (dd, J = 6.6–9.9 Hz, 1H, CHBr), 3.80 (dd, J = 4.0–9.9 Hz, 1H, CH'Br), 3.80 (s, 3H, OCH_3), 4.48 (m, 1H, H5), 6.93 (m, 2H, Harom.), 7.37 (m, 1H, Harom.), 7.77 (d, J = 7.7 Hz, 1H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 28.6, 39.1, 39.8, 56.3, 72.8, 112.1, 121.5, 125.2, 131.0, 132.4, 159.1, 176.8.

5-Bromomethyl-2-(3-methoxyphenyl)-3,4-dihydro-2H-pyrrole **(5c)**:
IR (neat): ν = 1610 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.90 (m, 1H, H4), 2.23 (m, 1H, H4'), 3.03 (m, 2H, H3), 3.60 (dd, J = 6.2–9.9 Hz, 1H, CHBr), 3.75 (dd, J = 4.0–9.9 Hz, 1H, CH'Br), 3.84 (s, 3H, OCH_3), 4.56 (m, 1H, H5), 6.96 (m, 1H, Harom.), 7.34 (m, 3H, Harom.).
^{13}C NMR δ: 26.8, 35.4, 38.0, 55.1, 72.8, 111.9, 116.8, 120.3, 129.1, 135.1, 159.3, 174.0.
MS (EI): m/z (%) = 269 (49) M + 2$^+$, 267 (50) M$^+$, 175 (35), 174 (75), 160 (100), 134 (73), 133 (78), 121 (29), 103 (36), 77 (33), 55 (32).

5-Bromomethyl-2-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrole **(5d)**:
IR (neat): ν = 1605 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.91 (m, 1H, H4), 2.26 (m, 1H, H4'), 3.03 (m, 2H, H3), 3.60 (dd, J = 6.6–9.9 Hz, 1H, CHBr), 3.79 (dd, J = 4.0–9.9 Hz, 1H, CH'Br), 3.85 (s, 3H, OCH_3), 4.56 (m, 1H, H5), 6.92 (d, J = 8.4 Hz, 2H, Harom.), 7.80 (d, J = 8.4 Hz, 2H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 27.3, 35.5, 38.4, 55.4, 73.0, 113.6, 127.4, 129.5, 162.0, 173.5.

5-Bromomethyl-2-(2-chlorophenyl)-3,4-dihydro-2H-pyrrole **(5e)**:
IR (neat): ν = 1615 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.92 (m, 1H, H4), 2.26 (m, 1H, H4'), 3.13 (m, 2H, H3), 3.71 (2dd, J = 6.2–6.0–9.9 Hz, 2H, CH_2Br), 4.58 (m, 1H, H5), 7.35 (m, 4H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 27.1, 36.4, 39.1, 73.1, 127.1, 128.5, 130.1, 130.7, 131.5, 134.5, 174.3.

5-Bromomethyl-2-(3-chlorophenyl)-3,4-dihydro-2H-pyrrole **(5f)**:
IR (neat): ν = 1615 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.90 (m, 1H, H4), 2.25 (m, 1H, H4'), 3.03 (m, 2H, H3), 3.65 (2dd, J = 6.0–6.2–9.9 Hz, 2H, CH_2Br), 4.60 (m, 1H, H5), 7.40 (m, 2H, Harom.), 7.84 (td, 1H, Harom.), 7.85 (t, J = 3.6 Hz, 1H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 25.5, 35.6, 38.1, 73.0, 125.9, 127.8, 129.7, 130.6, 134.5, 135.7, 173.2.
MS (EI): *m/z* (%) = 275 (22, M + 4$^+$), 273 (81, M + 2$^+$), 271 (65, M$^+$), 192 (43), 180 (91), 178 (100), 164 (51), 138 (51), 137 (24), 125 (21), 115 (20), 55 (43).

5-Bromomethyl-2-(4-chlorophenyl)-3,4-dihydro-2H-pyrrole **(5g)**:
IR (neat): ν = 1610 (C=N) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.93 (m, 1H, H4), 2.23 (m, 1H, H4'), 2.87 (m, 2H, H3), 3.55 (dd, J = 5.5–9.7 Hz, 1H, CHBr), 3.63 (dd, J = 4.2–9.7 Hz, 1H, CH'Br), 4.46 (m, 1H, H5), 7.26 (m, 2H, Harom.), 7.68 (m, 2H, Harom.).
^{13}C NMR ($CDCl_3$): δ = 27.4, 36.9, 38.2, 73.4, 128.2, 129.4, 133.6, 137.5, 173.2.

We would like to thank Dorothée Deuring for reviewing this manuscript.

(1) Clive, D.L.J.; Chiattu, G.; Curtis, N.; Kiel, W.A.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* **1977**, 725.
(2) Bartlett, P.A. In *Asymmetric Synthesis*, Morrison J. Ed.; Academic; Orlando, FL, 1984; pp 411–454.
(3) Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* **1979**, 171.
(4) For a review see:
Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
(5) For a review of the addition reaction to the cyano group and further heterocycle formation see:
Meyers, A.I.; Sircar, J.C. In *The Chemistry of the Cyano Group*; S. Patai, Ed.; Interscience: 1970; pp 341–422.
(6) Demoen, P.J.A.; Janssen, P.A.J. *J. Am. Chem. Soc.* **1959**, *81*, 6281.
Burckhalter, J.H.; Short, J.H. *J. Org. Chem.* **1958**, *23*, 1281.
Maginnity, P.M.; Cloke, J.B. *J. Am. Chem. Soc.* **1951**, *73*, 49.
(7) Pickard, P.L.; Tolbert, T.L. *J. Org. Chem.* **1961**, *26*, 4886.
(8) In entries 10, 11 no γ,δ-unsaturated ketones could be obtained by the usual acidic quenching of the Grignard adduct. This result indicates that Grignard addition to alkyl nitriles with or without an acidic hydrogen at the α position (entries 10 and 11 respectively) are not possible. Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, **1954**, pp 767–845.
(9) Such tautomerization has been reported; see: Bonnett, R.; Clark, V.M.; Giddey, A.; Todd, A. *J. Chem. Soc.* **1959**, 2087.
(10) Similar nitrogen bromination was detected in amide bromocyclization; see: Sakurai, O.; Takahashi, M.; Ogiku, T.; Hayashi, M.; Horikawa, H.; Iwasaki, T. *Tetrahedron Lett.* **1994**, *35*, 6317.