Reaction of Fischer alkynylcarbene complexes with 1-azadiene derivatives: unexpected formation of 3,4-dihydropyridines

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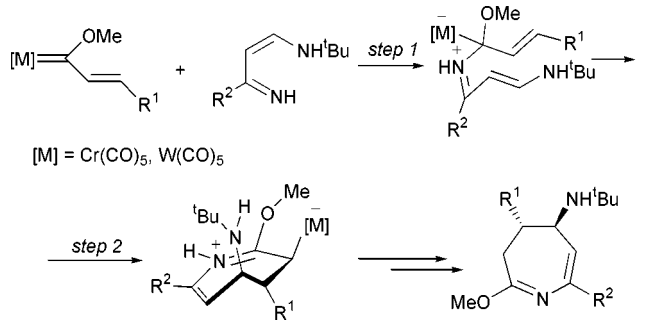
4-Amino-1-azabutadienes 2 underwent [3 + 3] cyclization with Fischer alkynylcarbene complexes of chromium and tungsten 1 to furnish high yields of substituted 3,4-dihydropyridines 3. The expected pyridine ring formation, which would result from cyclization/aromatization, does not take place. The process is thought to involve a 1,2-imidoyl group shift triggered by a 1,2-metal pentacarbonyl shift as the more characteristic steps. An X-ray diffraction experiment supports the proposed structure for the dihydropyridines.

Since their discovery in 1964 by Fischer,[1] stabilized Fischer carbene complexes of Group 6 have been recognized to play an important role in the construction of a variety of 3- to 7-membered rings and acyclic compounds. The reaction can occur either on the carbene ligand wherein the metal acts as reactivity and selectivity auxiliary, or at the metal center allowing a great number of cycloadditions in the coordination sphere.[2] Owing to their great potential, these complexes have frequently become also useful reagents in heterocyclic synthesis.

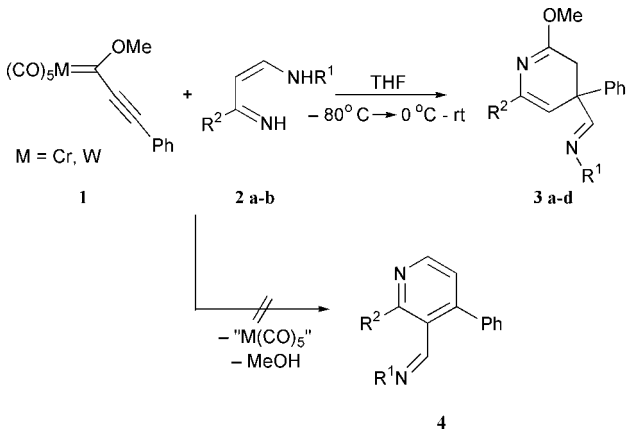
Particularly alkynylcarbene complexes[3] are appropriate precursors of heterocycles through a sequence involving addition and cyclization. In this field, several [3 + 2],[4] [4 + 2][5] and [4 + 3][6] *N*-heterocyclizations using alkynyl Fischer carbene complexes have been accomplished. On the contrary, [3 + 3] *N*-heterocyclizations are much less common and only a few examples are known.[7–9]

On the other hand, we recently discovered a novel reaction pathway for alkenyl- and alkynyl-carbene complexes towards unsaturated substrates.[6] This mechanism is exemplified in Scheme 1 for the [4 + 3] cycloaddition of alkenylcarbene complexes with 4-amino-1-azabutadienes giving azepines[6a] and consists in (i) 1,2 addition of the imine nitrogen to the carbene carbon (step 1) and 1,2-$(OC)_5M$ migration-promoted cyclization (step 2).



Scheme 1 Mechanism for the synthesis of azepines from 4-amino-1-azadienes and alkenyl Fischer carbene complexes.

Continuing our interest in the chemistry of azabutadiene derivatives and Fischer carbene complexes, we report herein the reaction of 4-amino-1-azadienes **2** with pentacarbonyl(1-methoxy-3-phenyl-2-propynylidene)-chromium and -tungsten complexes **1** leading to dihydropyridines **3**, wherein the imidoyl fragment of the azadiene is transferred to the metal-ligand fragment. Thus, azadiene derivatives **2** were mixed with chromium carbene complex **1a** (molar ratio 1 : 1) in THF at −20 °C and the mixture allowed to reach 0 (for $R^1 = Bu^t$) or 25 °C (for $R^1 = c\text{-}C_6H_{11}$). Column chromatography purification allowed us to isolate a single adduct. Surprisingly, the expected pyridine ring **4**[10] was not formed at all, but substituted 3,4-dihydropyridines **3** were obtained in high yields (Scheme 2, Table 1). Replacement of chromium complex **1a** with tungsten complex **1b** resulted neither in change of the reaction course nor in noticeable change of reaction yields.



Scheme 2 Synthesis of the 3,4-dihydropyridines **3** from alkynyl Fischer carbene complexes.

Table 1 Dihydropyridines **3** synthesized

Compound[a]	R^1	R^2	Yield (%)
3a	Bu^t	Ph	87
3b	Bu^t	$c\text{-}C_3H_5$	84
3c	Bu^t	$i\text{-}C_3H_5$	92
3d	$c\text{-}C_6H_{11}$	$4\text{-}MeC_6H_4$	58

[a] Isolated yields for M = Cr.

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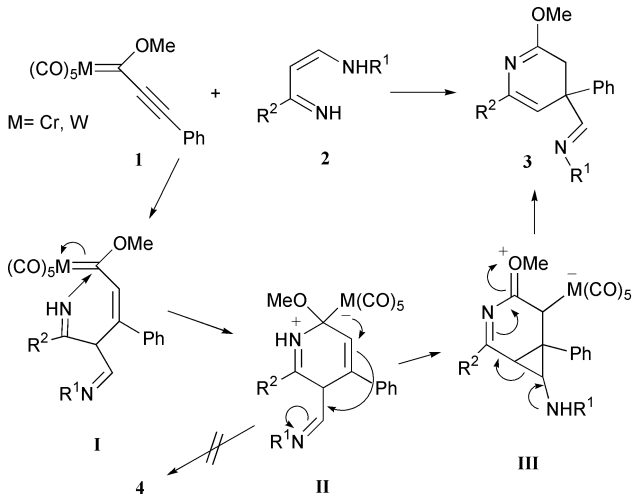
The spectroscopic data found are in concordance with structure **3**. Thus, the diastereotopic hydrogen atoms attached to the ring C3 appear as two doublets ($J = 16$ Hz) around δ 2.5 and 3.2 in the ^{1}H NMR spectra. Moreover, the more characteristic resonances in the ^{13}C NMR spectra are found at δ 166–167 (C2), 35–36 (C3), 48–49 (C4), 104–107 (C5), 145–153 (C6) and 154–159 (CH=N).

The structure of compounds **3** was unambiguously confirmed by an X-ray[11] diffraction experiment performed on **3d** (Fig. 1).

From a mechanistic point of view it is not easy to rationalize the formation of compounds **3**, specifically the observed 1,2-imidoyl rearrangement. The present proposal is based primarily on the mechanism shown in Scheme 1 along with the assumption that a cyclopropane intermediate participates (Scheme 3). The reaction must be initiated by Michael-type addition of the C_β–H enamine to form intermediate **I**. The second step would involve formation of the dihydropyridine intermediate **II** by intramolecular nitrogen addition to the metal carbene carbon. The key step is the formation of the cyclopropane species **III** by intramolecular 1,2-M(CO)$_5$ migration-promoted *anti* nucleophilic attack at the imine function. Finally, cyclopropane ring opening of **III** followed by hydrogen transfer and reductive metal elimination transforms **III** into the dihydropyridine ring **3**.

In summary, we have shown that 4-amino-1-azabutadienes readily react with alkynylcarbene complexes under very mild reaction conditions affording high yields of 3,4-dihydropyridines, whose structure is certainly unusual.[12] This reaction features the following aspects: (i) a [3 + 3] *N*-heterocycloaddition that is rather uncommon in the field of carbene complexes, (ii) a 1,2-imidoyl shift which results in the formation of a quaternary center in preference to the expected cyclization to the pyridine ring and (iii) 1,2-metal migration.



Scheme 3 Proposed mechanism in the synthesis of the 3,4-dihydropyridines **3**.

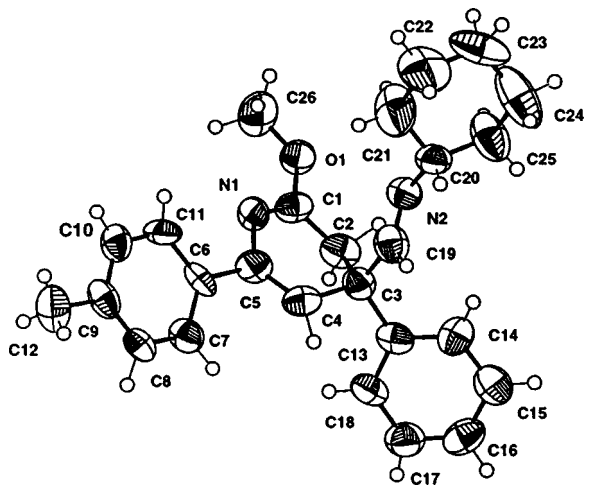


Fig. 1 Crystal structure of the 3,4-dihydropyridine **3d**.

Experimental

General methods

All reactions were carried out under a N_2 atmosphere. All common reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. THF was distilled from sodium–benzophenone under a N_2 atmosphere prior to use. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. NMR spectra were run on a Bruker AC-300 spectrometer.

Synthesis of 3,4-dihydropyridines 3a–3d

Over a 50 mL THF solution of the 4-amino-1-azabutadiene **2** (1.5 mmol) at −80 °C, 1.5 mmol of the alkynyl Fischer carbene complex **1** were added. The stirred solution was allowed to reach 0 °C for **3a**–**3c** and two additional days at room temperature for **3d**. Solvents were removed under vacuum and the residue was purified by chromatographic column over silica gel (hexane–triethylamine (10 : 1)).

4-*tert*-Butyliminomethyl-2-methoxy-4,6-diphenyl-3,4-dihydropyridine 3a. Yield 87%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.3 (s, 9H); 2.5 (d, 1H, $J = 15.9$); 3.4 (d, 1H, $J = 15.9$ Hz); 4.0 (s, 3H); 6.1 (s, 1H); 7.3–7.6 (m, 8H); 7.6 (s, 1H); 8.0 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2 (s); 154.4 (d); 145.0 (s); 143.3 (s); 138.5 (s); 128.6 (d); 128.1 (d); 127.8 (d); 126.9 (d); 126.8 (d); 125.5 (d); 107.5 (d); 56.6 (s); 53.1 (q); 48.6 (s); 35.4 (t); 29.4 (q). HRMS ($C_{23}H_{26}N_2O$): calculated *m/z* 346.20451, found 346.20379.

4-*tert*-Butyliminomethyl-6-cyclopropyl-2-methoxy-4-phenyl-3,4-dihydropyridine 3b. Yield 84%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.7 (m, 2H); 0.9 (m, 2H); 1.2 (s, 9H); 1.7 (m, 1H); 2.3 (d, 1H, $J = 16.0$); 3.2 (d, 1H, $J = 16.0$ Hz); 3.7 (s, 3H); 5.3 (s, 1H); 7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2 (s); 155.1 (d); 148.0 (s), 143.8 (s); 128.5 (d); 128.0 (d); 126.7 (d); 104.5 (d); 56.4 (s); 52.7 (q); 48.1 (s); 36.0 (t); 29.4 (q); 16.0 (d); 4.6 (t); 4.3 (t). HRMS ($C_{20}H_{26}N_2O$): calculated *m/z* 310.20451, found 310.20322.

4-*tert*-Butyliminomethyl-6-isopropyl-2-methoxy-4-phenyl-3,4-dihydropyridine 3c. Yield 92%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 6H, $J = 6.6$); 1.2 (s, 9H); 2.3 (d, 1H, $J = 16.2$); 2.5 (sp, 1H, $J = 6.6$); 3.15 (d, 1H, $J = 16.2$ Hz); 3.8 (s, 3H); 5.2 (s, 1H); 7.2–7.4 (m, 5H); 7.45 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (s); 155.0 (d); 153.9 (s); 143.8 (s); 128.5 (d); 126.8 (d); 126.7 (d); 103.7 (d); 56.3 (s); 52.7 (q); 47.7 (d); 35.8 (t); 34.5 (d); 29.4 (q); 20.9 (q).

4-Cyclohexyliminomethyl-2-methoxy-6-(4-methylphenyl)-4-phenyl-3,4-dihydropyridine 3d. Yield 58%. Solid. mp 77–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2–1.9 (m, 10H); 2.4 (s, 3H); 2.5 (d, 1H, $J = 15.9$); 3.1 (m, 1H); 3.25 (d, 1H, $J = 15.9$ Hz); 3.9 (s, 3H); 6.0 (s, 1H); 7.2–7.9 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (s); 158.7 (d); 145.1 (s); 143.0 (s); 137.6 (s); 135.7 (s); 128.8 (d); 128.6 (d); 127.0 (d); 126.9 (d); 125.4 (d); 106.5 (d); 68.7 (d); 53.1 (q); 48.6 (s); 35.6 (t); 34.2 (t); 34.0 (t); 25.6 (t); 24.5 (t); 24.3 (t); 21.1 (q). HRMS ($C_{26}H_{30}N_2O$): calculated *m/z* 386.23581, found 386.23558.

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10 The formation of this adduct would result from Michael-type addition followed by cyclization and aromatization.[7]
11 Crystal data for **3d**: $C_{26}H_{30}N_2O$, $M_r = 386.52$, orthorhombic, space group $Pbc2_1$, $a = 6.632(2)$, $b = 19.859(2)$, $c = 34.049(4)$ Å, $V = 4484(2)$ Å^3, $Z = 8$, Mo-Kα radiation (graphite crystal monochromator), $\lambda = 0.71073$ Å, $\mu = 0.069$ mm^{-1}, $T = 293(2)$ K. Final conventional $R = 0.0591$ (for 1368 $F_o > 4\sigma(F_o)$), and $wR2 = 0.2829$ (for all reflections). CCDC reference number 440/215. See http://www.rsc.org/suppdata/nj/b0/b005648k/ for crystallographic files in .cif format.
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