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First [4+2] Cycloaddition of Alkynyl Fischer Carbene Complexes with Heterodienes. Facile Synthesis of 1,4-Dihydropyridines from 1-Azadienes

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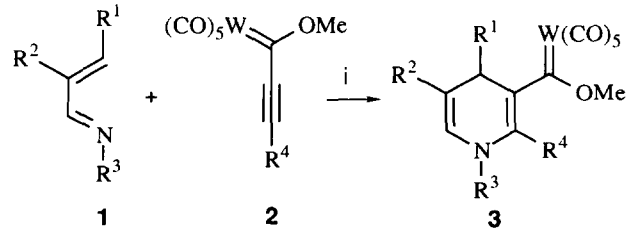
Abstract : Neutral 1-azadienes react in a [4 + 2] fashion with alkynyl Fischer carbene complexes to afford regioselectively substituted 1,4-dihydropyridines © 1997 Elsevier Science Ltd.

We have recently reported the reaction of 1-azadienes with chromium Fischer alkynyl carbene complexes that results in the formation of azepines through a clean [4 + 3] annulation.[1] In the course of that study we discovered that, in some cases, a small amount of the [4 + 2] cycloadduct was also obtained. We focussed on this observation since the reluctance of 1-azadienes to undergo [4 + 2] cycloadditions is very well documented. Although one example of cycloaddition of unactivated 1-azadiene with enamines has been reported,[2] their reaction with electron poor dienophiles is not expected and indeed, it remains unknown.[3] On the other hand, a range of [4 + 2] cycloadditions of activated carbodienes with alkynyl Fischer carbene complexes have been reported.[4] Having all this in mind, we thought that it would be important to find adequate conditions to direct the reaction towards the [4 + 2] process.[5] Here we report that neutral 1-azadienes react with tungsten Fischer alkynyl carbene complexes to afford, in a regioselective way, 1,4-dihydropyridines.

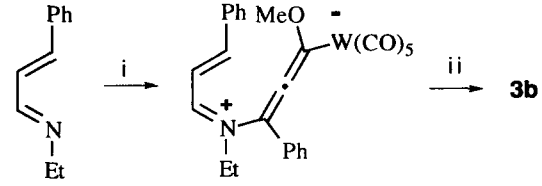
Thus, when simple 1-azadienes **1** were reacted at 20 °C in THF with pentacarbonyl(methoxy)alkynyltungsten carbene complexes **2** for 5 to 360 min, the [4 + 2] cycloadducts **3** were obtained in high yields after column chromatographic purification (Scheme 1, Table 1). The regiochemical assignments of compounds **3** were unequivocally made on the basis of their NMR data including long range C-H correlations.[6]



1 **2** **3**

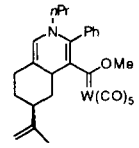
Scheme 1 *Reagents and conditions*: i) THF, 20 °C, 5-360 min

The reaction initiates through a Michael addition of the nitrogen lone pair to the conjugated triple bond of the complex with the formation of the allenic intermediate **4.** This reaction pathway was confirmed by an NMR experiment in THF_{d8} at -50 °C. Under these conditions, **4** could be unequivocally characterized by its spectroscopic data (δ_{CO}: 207.3; 203.2 ppm; $\delta_{C=C=C}$: 188.6; 162.4; 106.3 ppm).[7] Besides, when the temperature was raised to -10 °C, **4** quickly converted into **3a** (Scheme 2).



Scheme 2 *Reagents and conditions*: i) NMR tube, THF_{d8}, -50 °C; ii) -10 °C

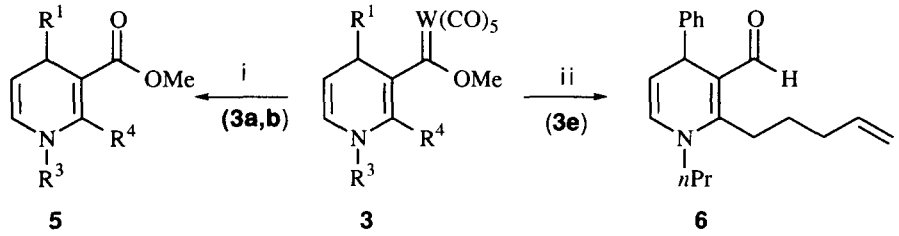
Table 1. 1,4-Dihydropyridines 3 Prepared from 1-Azadienes 1 and Carbene Complexes 2

Compound	R^1	R^2	R^3	R^4	t (min)	Yield (%)[a]
3a	Ph	H	*n*Pr	Ph	5[b]	87
3b	Ph	H	Et	Ph	5	89
3c	Ph	H	Bn	Ph	5	81
3d	Ph	H	*i*Pr	Me	60	67
3e	Me	H	CH_2=CH-CH_2	$SiMe_3$	360	68
3f	Ph	H	*n*Pr	$(CH_2)_3CH=CH_2$	60	89
3g	H	Me	*n*Pr	Ph	60	72
3h			 (2:1 diastereomeric mixture)		60	65

[a] Isolated yields (not optimized) after column chromatography. [b] In a control experiment azadiene and carbene complex were mixed in THF at r. t. An aliquot was taken 30 sec later, filtered over celite and the solvent removed; an NMR sample taken inmediately showed essentially the disappearance of the starting material and formation of pure cycloadduct **3a**.

From the data on Table 1 we can infer that the reaction is quite general as a wide variety of substituents can be attached to the pyridine system. The reaction proceeds under very smooth conditions and is, in general, fast, even when R^4 is a bulky group (**3d**, R^4 = $SiMe_3$). It is also worth to point out the 1,3-chirality induction observed in the case of the azadiene derived from (S)-(-)-perillaldehyde (**3g**).

Finally, dihydropyridinyl carbene complexes **3** can be easily demetallated to 3-methoxycarbonyldihydropyridines **5** by treatment with pyridine *N*-oxide in THF at room temperature.[8] On the other hand, heating of the complex **3e** in toluene at reflux resulted in the formation of the formyl derivative **6** after column chromatography purification (SiO_2, hexane/ethyl acetate, 4:1) (Scheme 3).



5 **3** **6**

Scheme 3 *Reagents and conditions*: i) THF, 20 °C, 6 h, pyridine *N*-oxide, 88% for **3a**, 93% for **3b**; ii) toluene, reflux, 2h, 78%.

In summary , we have shown that alkynyl Fischer carbene complexes behave as excellent dienophile partners and actually are the reagents of choice in order to achieve the elusive [4 + 2] cycloaddition of 1-azadienes. In addition, this process provides a very convenient entry into substituted 1,4-dihydropyridines, substrates of high relevance because of their multiple biological activities.[9] Encouraged by the noteworthy selectivity observed in the formation of pyridine **3g**, we are currently dedicating intensive work to devise an enantioselective version of this process.

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5 Previous reports from our group[10] and from Wulff[11] show the preference of tungsten carbene complexes to undergo [4 + 2] cycloadditions compared to the related chromium carbene complexes.

6. Spectroscopic data for **3a** ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.67 (t, ^3J(H,H) = 7.3 Hz, 3H, CH_3); 1.45 (m, 2H, CH_2); 2.96 (m, 2H, CH_2-N); 3.74 (s, 3H, OCH_3); 5.35 (dd, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 6.4 Hz, 1H, CH=C-N); 5.44 (d, ^3J(H,H) = 6.4 Hz, 1H, CHPh); 6.12 (d, ^3J(H,H) = 7.3 Hz, 1H, C=CH-N); 7.1-7.6 (m, 10Harom); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 311.0 (s), 202.1 (s), 197.8 (s), 147.1 (s), 137.8 (s), 136.2 (s), 130.9 (d), 130.3 (s), 128.6 (d), 128.3 (d), 128.1 (d), 127.9 (d), 127.6 (d), 126.9 (d), 126.3 (d), 107.4 (d), 67.4 (q), 52.4 (t), 45.4 (d), 23.4 (t), 10.8 (q); IR ($CDCl_3$): υ [cm^{-1}] = 1936, 2063; HRMS calculated for $C_{27}H_{23}NO_6W$: 641.1039, Found: 641.1027..

7. For Michael adducts of triphenylphosphine and alkynyl Fischer carbene complexes, see reference 12.

8. In an attempt to obtain directly the compound **5a**, we found that the reaction of azadiene **1** (R^1 = Ph, R^2 = H, R^3 = *n*Pr) with methyl phenylpropiolate acid in THF in a sealed tube at 120 °C for 7 days resulted only in quantitative recovering of the starting materials.

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