The First [4 + 3] Annulation of Fischer Carbene Complexes with Azadienes: Facile Synthesis of Azepines

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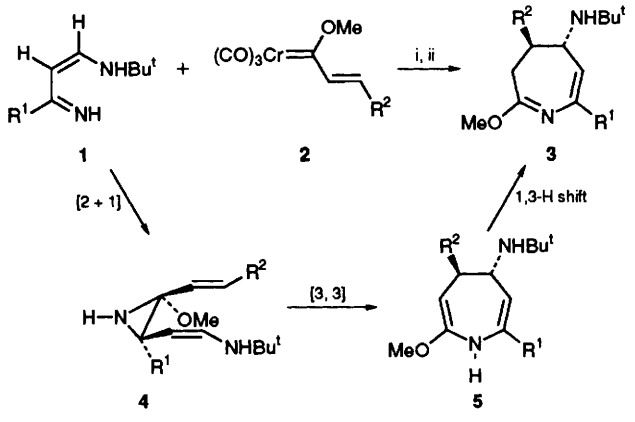
The reaction of 3-iminoprop-1-enylamines **1** with pentacarbonyl(1-methoxyprop-2-enylidene)chromium(0) complexes leads stereoselectively to substituted 5*H*-6,7-dihydroazepines in high yields; the process takes place at low temperature and is thought to involve a tandem imine cyclopropanation–Cope rearrangement.

Monocyclic medium ring nitrogen heterocycles are an extremely important class of compounds, which occur in a range of natural and unnatural products; in particular, azepines fall into this category of structures and there are a very limited number, no general methods of preparation.[1] In the last few years, an efficient route to seven-membered carbocycles consisting of a tandem cyclopropanation–Cope rearrangement has been developed;[2] for instance, Wulff[3] and us[4] have reported the reaction of electron-rich dienes with α,β-unsaturated Fischer carbene complexes leading to substituted cycloheptadienes. Moreover, we have been able to achieve the first asymmetric synthesis of functionalized cycloheptane derivatives by using chiral 2-aminobutadienes.[4b] In this regard, we have employed for the first time heterodienes and we describe herein the preliminary results on the reaction of electon-rich 3-iminoprop-1-enylamines **1** with α,β-unsaturated Fischer carbene complexes **2** as an efficient entry into functionalized azepines.

3-Iminoprop-1-enylamines **1** were prepared by addition of the lithiated *N*-(*tert*-butyl) ethylidene amine to the corresponding nitrile R^1CN.[5] Then, **1** (1.5 mmol) in THF (tetrahydrofuran) (5 ml) was added to a solution of the chromium complex **2** (1.5 mmol) in THF (40 ml) at −78 °C; the reaction mixture was allowed to reach −40 °C during 3 h, treated with silica gel for 3 h and filtered. Removing the solvents gave crude compounds **3** in excellent yields and with high purity; heterocycles **3** were further purified by flash column chromatography (SiO_2, hexane–triethylamine 10:1) (Scheme 1), (Table 1).‡



Scheme 1 *Reagents and conditions*: i, THF, −78 °C → −40 °C, 3 h; ii, SiO_2, THF–diethyl ether, 25 °C, 3 h

Table 1 5*H*-6,7-Dihydroazepines **3**

Compd.[a]	R^1	R^2	Yield (%)[b]
3a	*c*-C_3H_5	Ph	90
3b	*c*-C_3H_5	2-Furyl	80
3c	Et	Ph	91
3d	*p*-Tolyl	2-Furyl	62
3e	Ph	Ph	70
3f	4-Cl-C_6H_4	Ph	52

[a] All new compounds reported here gave satisfactory analytical figures. [b] Overall yield of purified products **3** from iminopropenes **1**.

Azepines **3** were formed as sole stereoisomers according to the ^1H NMR (300 MHz) data of the reaction crude. The *trans*-stereochemical relationship of **3** was deduced from NOE (nuclear Overhauser enhancement) experiments.

The tandem imine cyclopropanation–[3,3] sigmatropic rearrangement accounts well for the results observed in the reaction. Thus, initial stereoselective cyclopropanation of the azadiene **1** through its unsubstituted imine function would form the *cis*-divinylazacyclopropane **4**; aza-Cope rearrangement of the latter would lead to unstable 1*H*-azepine **5**, which tautomerises to **3** by hydrogen shifts. The exclusive formation of the diastereoisomer **4** is noteworthy and is probably a consequence of complexation of $Cr(CO)_4$ to both olefin and enamine groups.§

The regioisomeric cycloadduct **6**, which would arise from cyclopropanation of the electron-rich carbon-carbon double bond of **1** followed by [3,3]-aza-Cope rearrangement, was not detected in the reaction crude. The structure **3** was preferred to **6** on the basis of NMR¶ and confirmed by acid hydrolysis (Scheme 2); thus, treatment of either the crude mixture of the reaction of **1** (R^1 = *c*-C_3H_5) with **2** (R^2 = furyl) or the isolated azepine **3b** with diluted HCl followed by column chromatography resulted in the isolation of the expected ε-ketoesters **7** and (*E*)-**8** (*J* = 15.9 Hz) (ratio of *ca.* 1:2) instead of the 1,6-diketone that would be formed from **6**.

In summary, we have shown for the first time that heterodienes, *e.g.* 3-iminoprop-1-enylamines, undergo efficiently regio- and stereo-selective [4 + 3] cycloaddition with α,β-unsaturated Fischer chromium carbene complexes at temperatures as low as −40 °C, making this process a very facile entry into substituted azepines. The process probably initiates by cyclopropanation of the unsubstituted imine group, which has no precedents in the literature.‖ Because of the very mild reaction conditions required, work directed to explore the applicability of this process to the asymmetric synthesis of azepines is under way.**

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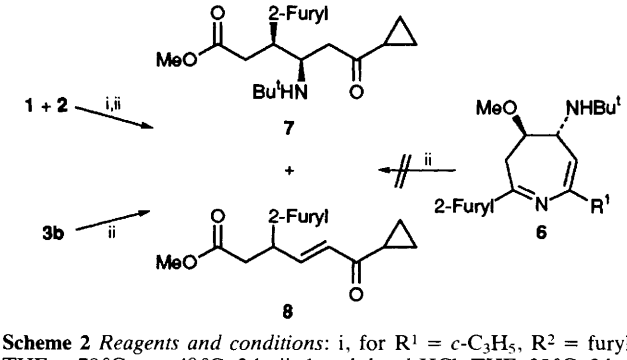

Scheme 2 *Reagents and conditions*: i, for R^1 = *c*-C_3H_5, R^2 = furyl; THF, −78 °C → −40 °C, 3 h; ii, 1 mol dm^{-1} HCl, THF, 25 °C, 3 h

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Footnotes

† Servicio Resonancia.

‡ Elemental analyses and spectroscopic data, including homonuclear and heteronuclear correlation NMR experiments, were in agreement with the structures assigned.

Spectroscopic data for compound **3a**: ^{1}H NMR ($CDCl_3$; 300 MHz); δ 0.35 (m, 1H), 0.55 (m, 2H), 0.8 (s, 9H), 0.85 (m, 1H), 1.5 (m, 1H), 2.2 (dd, 1H, *J* 13.2 and 0.8 Hz), 2.8 (dd, 1H, *J* 13.2 and 9.0 Hz), 3.25 (m, 1H), 3.35 (dd, 1H, *J* 11.6 and 4.5 Hz), 3.8 (s, 3H), 5.35 (d, 1H, *J* 4.5 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$; 75 MHz); δ 168.7(s), 145.8(s), 143.3(s), 128.5(d), 127.3(d), 127.0(d), 117.8(d), 60.1(d), 55.0(d), 53.1(q), 50.5(s), 35.3 (t), 29.3 (q), 15.5 (d), 4.5 (t) and 3.6 (t); MS *m/z* 312 (M^+) (Found: M^+, 312.2195. $C_{20}H_{28}N_2O$ requires M, 312.2201).

§ The cyclopropanation may involve zwitterionic species; intermediates of this type have been postulated by Wulff *et al* in the reaction of *N*-substituted imines with Fischer carbene complexes.[6] Attempts were also carried out to evidence the aziridine formation by using chromium carbene complexes lacking the vinyl function, *e.g.* methyl and phenyl carbene complexes, but neither azacyclopropane derivatives nor other structures derived therefrom could be isolated.

¶ The correlation of the methoxy hydrogen atoms with the most deshielded carbon atom in the 2D HMBC[7] spectrum rules out the structure **6**. On the other hand, the long-range connections derived from the aliphatic protons clearly established the seven-membered ring nature of **3**

Spectroscopic data for compound **8**: ^{1}H NMR ($CDCl_3$; 300 MHz); δ 0.9–0.95 (m, 2H), 1.05–1.1 (m, 2H), 2.1–2.2 (m, 1H), 2.75 (dd, 1H, *J* 15.9 and 8.2 Hz), 2.9 (dd, 1H, *J* 15.9 and 6.9 Hz), 3.7 (s, 3H), 4.1–4.2 (m, 1H), 6.1 (m, 1H), 6.25 (dd, 1H, *J* 15.9 and 1.3 Hz), 6.3–6.35 (m, 1H), 6.9 (dd, 1H, *J* 15.9 and 7.3 Hz), 7.35 (m, 1H); ^{13}C NMR ($CDCl_3$; 75 MHz); δ 199.9 (s), 171.2 (s), 153.1 (s), 143.4 (d), 142.0 (d), 130.8 (d), 110.2 (d), 106.0 (d), 51.8 (q), 37.8 (d), 37.1 (t), 19.0 (d), 11.4 (t); MS *m/z* 248 (M^+).

‖ Unsubstituted imines[8] and *N*-alkylimines[6] react with Fischer chromium carbene complexes yielding exchange and metathesis products, respectively.

** After we submitted this manuscript Aumann *et al.* reported the reaction of 4-methylamino-2-methyliminopent-3-ene with pentacarbonyl(1-ethoxy-3-phenylprop-2-ynylidene)tungsten leading to the pyridine ring.[9]

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