

Diene Tricarbonyl Iron Complexes Bearing a Free Diazo Group. III.¹ Synthesis of Pyrazoles and Chiral Complexes with α -Aminoacid or Dienylcyclopropane Substructures by 1,3-Dipolar Cycloaddition Reactions.

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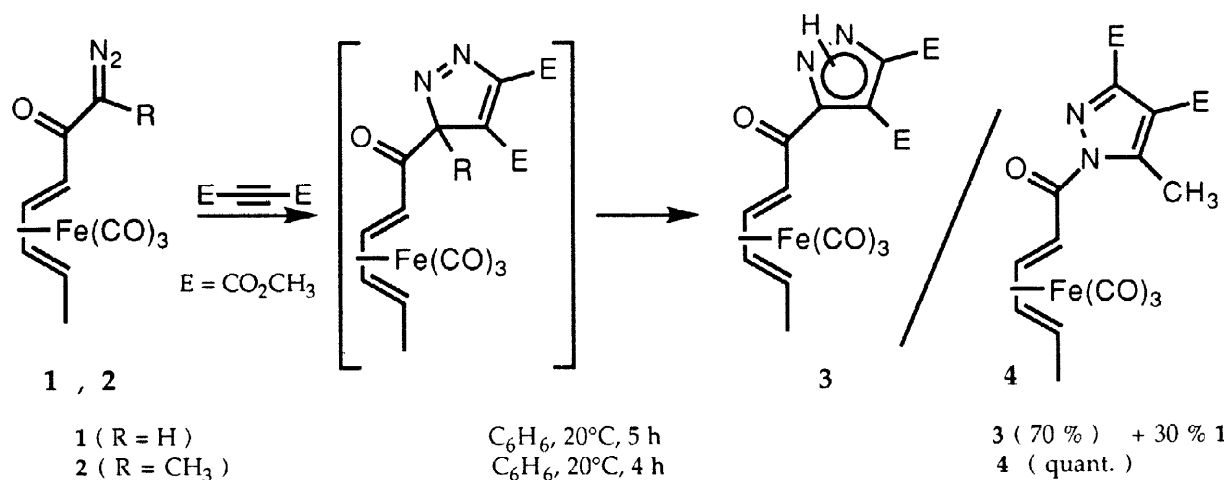
Abstract : Cycloaddition reactions of acetylenic and olefinic dipolarophiles with diazoketones and a diazoester linked to tricarbonyl iron coordinated diene units were investigated. 1H-pyrazoles were obtained directly from acetylene carboxylic esters by [1,5] group migrations at the stage of the primary formed 3H-pyrazoles. With methyl acrylate, the cycloaddition led to complexes of Δ^2 -pyrazolines and at slightly more elevated temperature, with the diazoester, to cyclopropane esters. All diastereomers formed in each reaction could easily be separated by simple chromatography on silica gel, illustrating one of the practical advantages of the use of tricarbonyl iron complexes. In the optically active series, this allowed the high ee synthesis of various products with α -aminoacid or dienylcyclopropane substructures.

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In two previous communications we have described the synthesis and some reactions as carbene precursors of diene tricarbonyl iron complexes bearing a free diazoketone¹ or diazoester group.² Such (chiral) diazocompounds are also potentially interesting reagents for 1,3-dipolar cycloadditions, since the corresponding *non complexed* diazocompounds are not easy to prepare (intramolecular reactions).

In this communication we describe some typical 1,3-dipolar cycloaddition and consecutive reactions of both types of diazo complexes, with acetylenic and olefinic dipolarophiles.

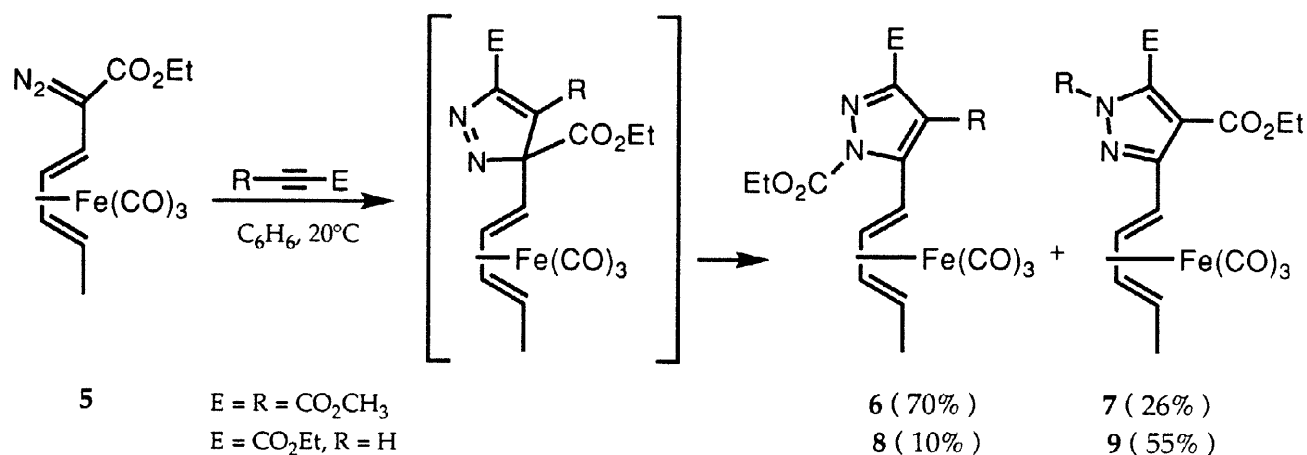
With the acetylenic dipolarophile DMAD (dimethyl acetylene dicarboxylate), the diazoketone complexes **1** and **2**³ reacted to give directly stable 1H-pyrazoles resulting from [1,5] migrations.



In the first case, the expected pyrazole **3** was formed, whereas an acyl shift led to the N-acyl pyrazole **4** in the case of the more reactive disubstituted diazoketone **2**.

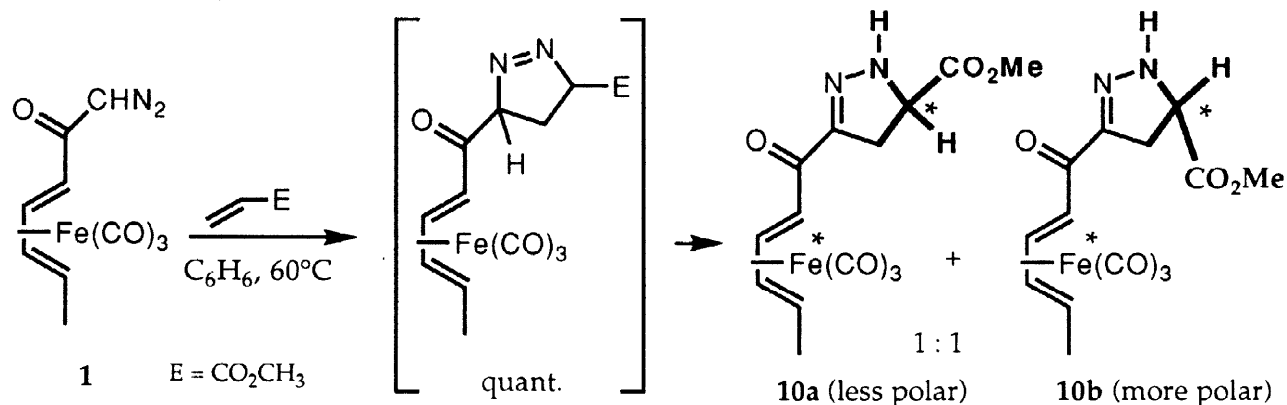
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The diazoester complex **5**, with the diazo group directly adjacent to the iron coordinated diene unit, reacted smoothly at room temperature with the acetylenic dipolarophiles DMAD and ethyl propynoate to give also 1H-pyrazoles resulting from rearrangements of the primary formed 3H-pyrazoles.



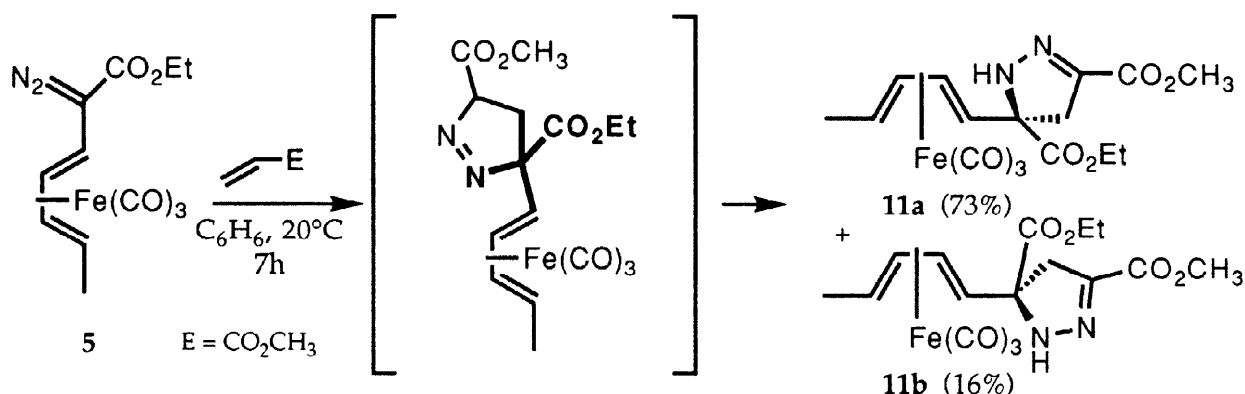
The observed rearrangements of the primary cycloadducts are not fundamentally different from those observed with similar, non organometallic, diazoketones. So the diazoketones **1** and **2** led to 1H-pyrazoles by prototropy or [1,5] H shift when an hydrogen is present, or to N-acylpyrazoles when not ([1,5] migration of the acyl group⁴). The situation is more complex with the diazoester **5**, where the ethoxycarbonyl group undergoes competitive [1,5] migrations to nitrogen *and* to carbon. In comparison, the dipolar cycloadditions with diazo-2-propionate led also predominantly to a [1,5] migration to carbon with ethyl propynoate as dipolarophile, but only to a [1,5] migration to nitrogen with DMAD.⁵ In the present case, the C-migration product, **7**, was also obtained (26 % isolated).⁶ This may be due to the steric decompression which goes with the [1,5] C-migration of the ethoxycarbonyl group. The [1,5] N-migration is sterically less favourable, since at the beginning the migrating group must come close to the carbonyls of the Fe(CO)₃ group.

Methyl acrylate was reacted as an olefinic dipolarophile with the diazoketone **1** and the diazoester **5**. In the first case, two diastereomeric Δ^2 -pyrazolines **10a** and **10b**⁷ were nearly quantitatively obtained in an approximate 1 to 1 ratio. The cycloaddition reaction is therefore almost unstereoselective, but, remarkably, *the diastereomers formed are very easily separable by simple chromatography on SiO₂ (R_F 0.39 and 0.28, hexane with 20 % EtOAc).*

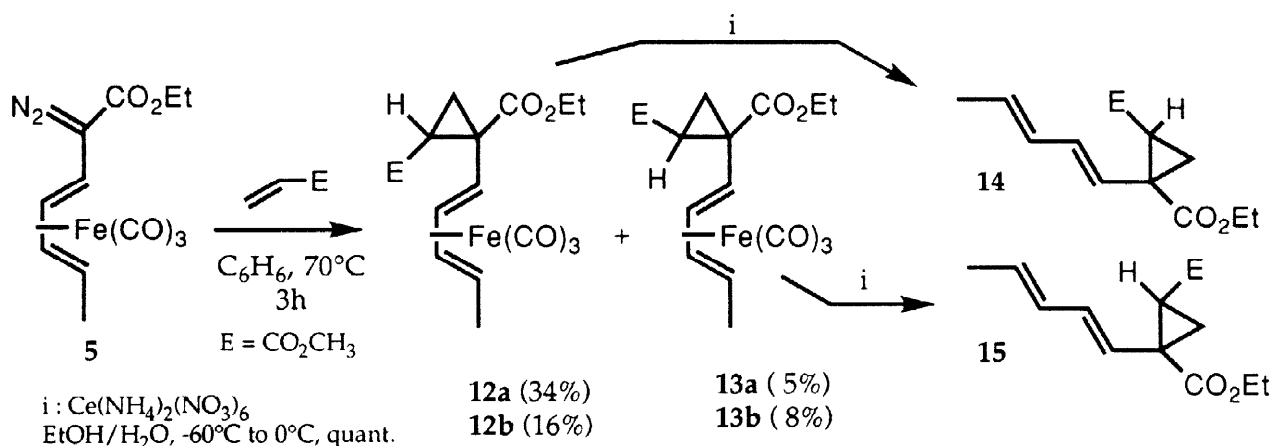


In the optically active series,⁸ this approach allowed an easy access to chiral products of high ee with an α -amino acid substructure ((-)-**1** \rightarrow (-)-**10a** (48 %, [α]_D = -294) and (+)-**10b** (44 %, [α]_D = +111) ; (+)-**1** \rightarrow (+)-**10a** (45 %, [α]_D = +297) and (-)-**10b** (47 %, [α]_D = -109)).

With the diazoester **5**, methyl acrylate led to two types of products, depending on the temperature. At room temperature, the easily separable Δ^2 -pyrazolines **11a** and **11b**, also with α -amino acid substructures, were obtained (chromatography on SiO_2 , R_F 0.32 and 0.19, hexane with 20 % EtOAc), the cycloaddition being stereoselective⁹ (less polar **11a** 73 %, more polar **11b** 16 %, along with ca. 5 % cyclopropanic compounds (vide infra)).



At more elevated temperature (70° C) the Δ^2 -pyrazolines were formed in only ca. 5 % yield, but four cyclopropanic diesters were now obtained (**12a**, **12b**, **13a** and **13b**) along with ca. 20 % of the much more polar monomolecular decomposition products of the diazo compound.² All compounds could be completely separated by simple column chromatography on SiO_2 , illustrating thus one of the great advantages of the stoichiometric use of stable metal π -complexes for the synthesis of enantiomerically pure compounds.



The two less polar products **12a**¹⁰ and **12b** (R_F 0.60 and 0.54, SiO_2 , hexane with 20 % EtOAc) gave the same cyclopropanic *trans*-diester **14** by quantitative decomplexation with Ce^{IV} ammonium nitrate, the more polar products **13a** and **13b** (R_F 0.39 and 0.33) leading to the *cis*-cyclopropanic diester **15**. By comparison of the ratio of the isolated diastereomeric Δ^2 -pyrazolines (**11a** 73 % / **11b** 16 %) and the ratio of the diastereomeric cyclopropanic diesters formed (34 % *trans* + 5 % *cis* / 16 % *trans* + 8 % *cis* or 34 % *trans* + 8 % *cis* / 16 % *trans* + 5 % *cis*) it is obvious that the cyclization resulting from thermal cleavage of nitrogen from the primary formed Δ^1 -pyrazolines is not a stereospecific process.¹¹ This can be advantageous since the good separation by chromatography of the products allows therefore a rapid synthesis of all possible diastereomers. In the optically active series⁸ pure enantiomers become thus available : (+)-**2** \rightarrow (-)-**12a** (51 %, $[\alpha]_D = -28$), (-)-**12b** (13 %, $[\alpha]_D = -67$), (-)-**13a** (16 %, $[\alpha]_D = -65$) and (+)-**13b** (18 %, $[\alpha]_D = +58$) ; (-)-**2** \rightarrow (+)-**12a** (47 %, $[\alpha]_D = +20$), (+)-**12b** (15 %, $[\alpha]_D = +69$), (+)-**13a** (11 %, $[\alpha]_D = +66$) and (-)-**13b** (10 %, $[\alpha]_D = -51$).¹²

Last, but not least, the diene $\text{Fe}(\text{CO})_3$ unit is a masked formyl or vinylogous formyl group (decomplexation + ozonolysis)¹³ thus enhancing the synthetic potential of the cycloaddition reactions described.

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References :

1. Franck-Neumann, M.; Geoffroy, P.; Winling, A. *Tetrahedron Lett.*, **1995**, 36, 8213.
2. Franck-Neumann, M.; Geoffroy, P.; Winling, A. *Synlett*, **1995**, 341.
3. Similarly to **1**, the diazoketone **2** was obtained in 30 % yield by treatment of the acid chloride of complexed sorbic acid with diazoethane (10 eq., ether, 0° C).
4. Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.*, **1972**, 937.
Franck-Neumann, M.; Buchecker, C. *Angew. Chem.*, **1973**, 85, 259.
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6. The pyrazole **7** results from a [1,5] migration of the ethoxycarbonyl group to the carbon, followed by a rapid [1,3] migration to nitrogen¹⁴ of the sole methoxycarbonyl group. The structure of **7** is in agreement with the fact that by treatment with acids or even by chromatography on SiO_2 , only a methoxycarbonyl group is cleaved. The structure of the main transposition product **6** was secured by X-ray diffraction, the details of which will be given in the full paper.
7. (-)-**10a** : $\text{C}_{14}\text{H}_{14}\text{FeN}_2\text{O}_2$ (C, H, N), orange solid $F = 89^\circ \text{C}$; $[\alpha]_D = -294$ (CHCl_3 , $c = 0.15$) ; IR (CCl_4 , cm^{-1}) : ν ($\text{C}\equiv\text{O}$) 1978, 1997, 2056, ν ($\text{C}=\text{O}$) 1744, ν ($\text{C}=\text{N}$) 1632 ; $^1\text{H-NMR}$ (CDCl_3 , 200 MHz, ppm/TMS, J) : $\delta = 1.48$ (d, 3H, 6.2 Hz), 1.70 (m, 1H), 2.25 (d, 1H, 8.5 Hz), 3.15 (dd, 1H, 17.7 and 11.8 Hz), 3.25 (dd, 1H, 17.7 and 6.1 Hz), 3.75 (s, 3H), 4.45 (dd, 1H, 11.8 and 6.1), 5.26 (m, 1H), 5.86 (dd, 1H, 8.5 and 5.0 Hz), 6.66 (s, 1H).
8. The optically active diazoketone complexes (-)-**1** and (+)-**1** (ee > 96 %, $^1\text{H-NMR}$ in the presence of $\text{Eu}(\text{tfc})_3$) were prepared from (-)-(2R,5S)-2,4-hexadien-1-oic acid $\text{Fe}(\text{CO})_3$ and (+)-(2S,5R)-2,4-hexadien-1-oic acid $\text{Fe}(\text{CO})_3$, respectively, similarly to the racemic compound.¹ The optically active acids were obtained by resolution via their diastereomeric esters with (-)-(S)-ethyl lactate¹⁵ : (-)-**1** : $[\alpha]_D = -520$ (CHCl_3 , $c = 0.2$) ; (+)-**1** : $[\alpha]_D = +512$ (CHCl_3 , $c = 0.7$). The optically active complexes (+)-**5** and (-)-**5** were obtained similarly to the racemic compound,² by Friedel-Crafts acylation of the optically pure piperylene complexes¹⁵ with ethyl oxalyl chloride followed by formation of the tosylhydrazone and Bamford-Stevens reaction : (+) ethyl (3S,6R)-2-diazo-3,5-heptadien-1-oate : (+)-**5** : $[\alpha]_D = 1065$ (CH_2Cl_2 , $c = 0.7$) ; (-) ethyl (3R,6S)-2-diazo-3,5-heptadien-1-oate : (-)-**5** : $[\alpha]_D = -1071$ (CH_2Cl_2 , $c = 0.7$).
9. The configurations of the adducts **11a** and **11b** are tentatively indicated, based on the hypothesis that the dipolarophile is approaching from the *exo* side, the preferred conformation for the diazo group in respect to the coordinated C = C bond being probably *s-cis* (linear N_2 smaller than CO_2Et).
10. (-)-**12a** : $\text{C}_{16}\text{H}_{18}\text{FeO}_7$ (C, H), brown oil ; $[\alpha]_D = -28$ (CH_2Cl_2 , $c = 0.8$) ; IR (CCl_4 , cm^{-1}) : ν ($\text{C}\equiv\text{O}$) 1962, 2045, ν ($\text{C}=\text{O}$) 1723 ; $^1\text{H-NMR}$ (CDCl_3 , 200 MHz, ppm/TMS, J) : $\delta = 1.11$ (d, 1H, 9.8 Hz), 1.12 (m, 1H), 1.25 (t, 3H, 7.1 Hz), 1.38 (d, 3H, 6.2 Hz), 1.46 (dd, 1H, 7.1 and 4.8 Hz), 2.07 (dd, 1H, 8.8 and 4.8 Hz), 2.33 (dd, 1H, 8.8 and 7.1 Hz), 3.67 (s, 3H), 4.11 (m, 2H), 4.98 (dd, 1H, 8.8 and 5.2 Hz), 6.12 (dd, 1H, 9.5 and 5.2 Hz).
11. The tricarbonyl iron dienyl substituent labilizes apparently greatly these Δ^1 -pyrazolines, since evolution of nitrogen is unexpected at such low temperatures with two symmetrically distributed electron withdrawing substituents. This originates probably from the stabilization of the intermediate radicals by a captodative effect.
12. The thermolysis was performed at 30° C for 24 h instead of 70° C for 3 h for the racemic complex. This explains the differences in yields observed and the better overall yield, since at 30° C only traces of monomolecular decomposition products are observed.
13. cf. Franck-Neumann, M.; Bissinger, P.; Geoffroy, P. *Tetrahedron Lett.*, **1997**, 38, 4473.
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