Tetrahedron Letters No. 32, pp 2965 - 2968.

0040-4039/79/0801-2965$02.00/0

PREPARATION OF N-CARBOMETHOXYAMINOPYRROLES

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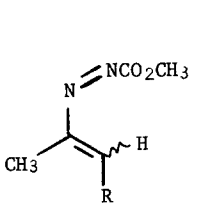
Azoalkenes 1 react with enamines and β-dicarbonyl compounds to give N-carbomethoxyaminopyrroles rather than N-carbomethoxy-1,2-dihydropyridazines.

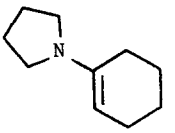
In connection with a proposed Diels-Alder based aromatic ring synthesis, we noted with interest recent reports of the synthesis of 1,2-dihydropyridazines from azoalkene precursors. Thus, the preparation of 2a by reaction of the morpholine enamine of cyclohexanone with azoalkene 1a has been described by Sommer;[1] Brodka and Simon have reported the isolation of dihydropyridazine 4a from the reaction of ethyl acetoacetate with azoalkene 3a.[2] Consequently, we expected that the isomeric dihydropyridazines 2b and 4b should be available from 1b and 3b, respectively (Chart 1). This, however, is not the case. Instead, a single crystalline material is isolated from both reactions; mp 114-115°C; λ_{max} (CH_3OH), 219 (ε 1.4 x 10^4), 231 (ε 1.1 x 10^4) and 267 nm (ε 4.3 x 10^3); 85% yield via path a, 15% yield via path b.

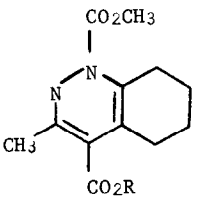
Dihydropyridazines 2b or 4b should be easily convertible to pyridazine 6. Decarbomethoxylation of the crystalline material noted above smoothly occurs with sodium cyanide in warm hexamethylphosphoramide.[3] The resulting product, however, resists oxidation to an aromatic ring.[4]

Chart 1



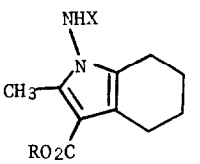
1a, R = CO_2CH_3
b, R = CO_2Et
c, R = C_6H_5





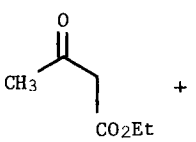
2a, R = CH_3
b, R = C_2H_5

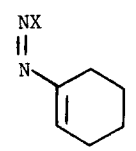
(a)



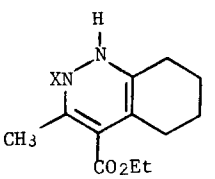
5a, X = CO_2CH_3; R = C_2H_5
b, X = H; R = C_2H_5
c, X = CO_2CH_3; R = CH_3

(b)

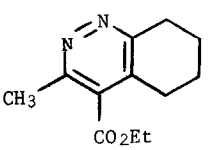




3a, X = p-$NO_2C_6H_4$
b, X = CO_2CH_3



4a, X = p-$NO_2C_6H_4$
b, X = CO_2CH_3



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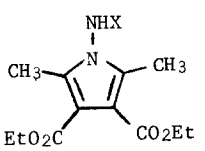
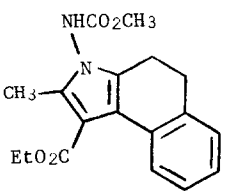


7a, X = CO_2CH_3
b, X = H



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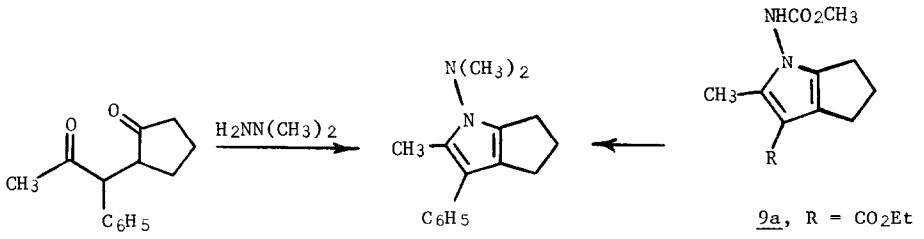
Reaction of azoalkene 1b[5] with ethyl acetoacetate gives a crystalline product (mp 129-130°C, 90% yield), which displays a very simple proton NMR spectrum; δ 1.30 (6H, triplet, J = 7.0 Hz), 2.13 (6H, singlet), 3.79 (3H, singlet), 4.28 (4H, quartet, J = 7.0 Hz) and 8.4 (1H, broad singlet). Treatment of this material with sodium cyanide in warm hexamethylphosphoramide gives a product identical to the previously reported N-aminopyrrole 7b.[6] Thus, the product obtained from the reaction of ethyl acetoacetate with 1b must be the pyrrole 7a, and that derived from azoalkenes 1b and 3b must be 5a. Furthermore, it is now clear that Sommer's compound 2a must be reformulated as 5c.

Azoalkene 1b can be used to construct a variety of N-aminopyrroles. For example, 8 (mp 155-157°C, 72% yield) is available from the pyrrolidine enamine of β-tetralone, and 9a (mp 116-118°C, 76% yield) from the pyrrolidine enamine of cyclopentanone.



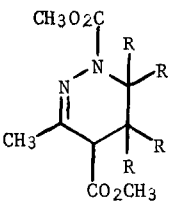
10 11

9a, R = CO_2Et
b, R = C_6H_5

We also have studied the reactivity of azoalkene 1c (prepared by dehydrobromination of the carbomethoxyhydrazone of 1-bromo phenylacetone; 1 N Na_2CO_3 in ether, red oil, 84% yield). Both β-dicarbonyl compounds and enamines react with 1c to give N-carbomethoxyaminopyrroles in high yield (e.g., 9b, 61% yield).[8] In order to unambiguously assign structure to 9b, we prepared 11 from diketone 10[9] and demonstrated that 11 was identical to that prepared from 9b by methylation (CH_3I, KOH, DMSO) followed by lithium aluminum hydride reduction (4 equiv, DME, reflux).

With the pyrrole structures clearly established, the question of mechanism of formation must be confronted. Sommer suggests that 1a reacts with olefins and enol ethers in Diels-Alder fashion.[1] The resulting adducts clearly display IR absorption for the C=N group; thus, 12 seems an appropriate structural representation. Controlled reactions of 1a with enamines, however, give compounds displaying N-H and C=C IR absorption and these were assigned structure 13. No explanation for the surprising preference for formation of tautomer 13 was advanced.

When the reaction of 1b and the pyrrolidine enamine of cyclopentanone is performed in THF solution at -78°C, an intermediate may be isolated in near quantitative yield; proton NMR δ 1.32 (3H, triplet, J = 7.0 Hz), 1.45-3.35 (15H, multiplet), 2.17 (3H, singlet), 3.75 (3H, singlet), 4.16 (2H, quartet, J = 7.0 Hz) and 6.85 (1H, broad singlet). Elimination of pyrrolidine from the intermediate to give 9a is conveniently carried out in refluxing THF-acetic acid solution. We suggest that the intermediate in this overall transformation corresponds to structure 14 rather than that analogous to 13.



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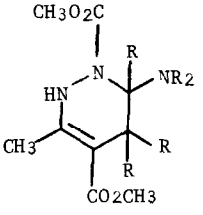
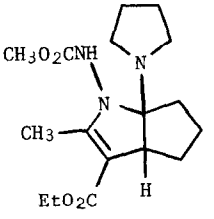


13



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In the following communication, we describe the use of N-carbomethoxyaminopyrroles in a versatile and high yield substituted benzene ring synthesis.

Acknowledgement[10]

This work was supported in part by the National Institutes of Health (Grant GM 26568).

References

1. S. Sommer, Chemistry Letters, 583 (1977); S. Sommer, Tetrahedron Letters, 117 (1977).
2. S. Brodka and H. Simon, Justus Liebigs Ann. Chem., 745, 193 (1971).
3. P. Miller and B. Siegfried, Tetrahedron Letters, 3565 (1973).
4. Dihydropyridazines are relatively unstable and are oxidized to pyridazines on exposure to air; see Heterocyclic Chemistry, A. Albert, Oxford University Press, Inc., Bristol, 1959, p. 113.
5. For details of the synthesis of 3b, see A. G. Schultz and W. K. Hagmann, J. Org. Chem., 43, 3391 (1978). In general, reactions of azoalkenes with β-dicarbonyl compounds (1 equiv) or enamines (1.1 equiv) are performed in THF solution.
6. C. Bülow, Ber. 35, 4311 (1902).
7. N-aminopyrroles have been prepared by the reaction of semicarbazones of α-haloketones with β-diketones and base; V. Spiro and P. Madonia, Ann. Chim. (Italy), 50, 1971 (1960). Presumably, an azoalkene is an intermediate. For additional work in this area, see L. Bernardi, P. Masi and G. Rosini, Ann. Chim. (Rome), 63, 601 (1973).
8. Compounds 5a, 7a, 8, and 9a gave satisfactory elemental analyses.
9. Diketone 10 is prepared in modest yield by the reaction of 1-bromo phenylacetone with the pyrrolidine enamine of cyclopentanone. For the conversion of 1,4-diketones to N-dialkylaminopyrroles, see H. S. Broadbent, W. S. Burnham, R. K. Olsen, and R. M. Sheeley J. Heterocyclic Chem., 5, 757 (1968).
10. This work was initiated in the Chemistry Department of Cornell University.

(Received in USA 18 April 1979)