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AZETIDINES AND 1-PYRROLINES FROM AN ELECTRON-DEFICIENT ALLENE AND C=N COMPOUNDS

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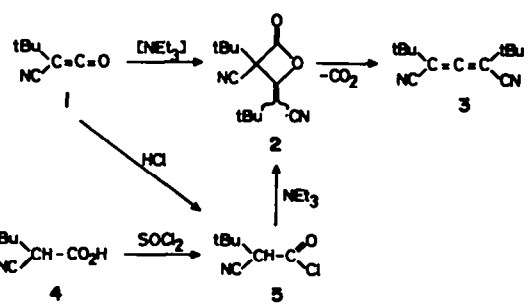
Abstract—The (2+2) cycloadditions of 1,3-di-t-butylallene-1,3-dicarbonitrile (3) to azomethines or an acyclic amidine afford 2-alkylidene azetidines **12**, **19**. In the reaction of 3 with the 3-dimethylamino-2H-azirine **20** the 1,2 bond of the 3-membered ring is cleaved to give the stereoisomeric 1-pyrrolines **23**.

The cycloaddition chemistry of simple allenes can be understood in terms of concerted or diradical mechanisms.[1] However, allenes carrying electron-donating[2-5] or electron-withdrawing substituents[6,7] react as typical nucleophiles or electrophiles, and their cycloadditions probably involve zwitterionic intermediates. In fact, stable dipoles could be isolated in some examples with exceptional mesomeric stabilization of the charges.[2,3,5] Surprisingly, only a limited choice of reaction partners has been employed in the cycloadditions so far. As for C=N systems, isocyanates[2,4,8] and a carbodiimide[5] are the only examples. Reactions of electrophilic allenes with non-cumulated C=N compounds have not been reported, although they can be anticipated to provide a convenient access to interesting nitrogen heterocycles. This assumption is verified in the present study, which is based on 1,3-di-t-butylallene-1,3-dicarbonitrile (3). This allene was selected for comparison with the well-documented[9] cycloadditions of the corresponding keten 1 to C=N systems.

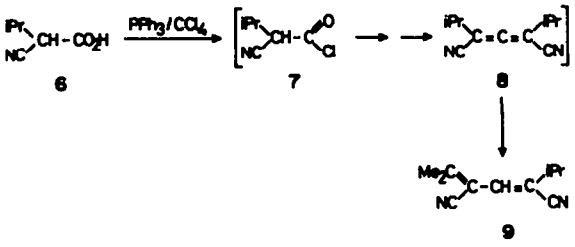
RESULTS AND DISCUSSION

Synthesis of the allene 3. According to the procedures of Moore and Duncan,[10] the allene 3 can be prepared starting from the keten 1. In one approach, the keten is induced to dimerize under the catalytic influence of triethylamine resulting in the formation of the oxetanone 2, which easily eliminates carbon dioxide and thus affords the allene 3. Alternatively, hydrogen chloride is added to 1, and the acyl chloride 5 formed *in situ* is again treated with triethylamine (Scheme 1). We found that the chloride 5 can be more conveniently prepared from the readily accessible[11] acid 4 and thionyl chloride. However, treatment of 4 with the reagent triphenylphosphine/tetrachloromethane, which is recommended as a particularly mild procedure for the conversion of carboxylic acids into their chlorides,[12] in our hands gave a mixture of 3 and 5.



Scheme 1.

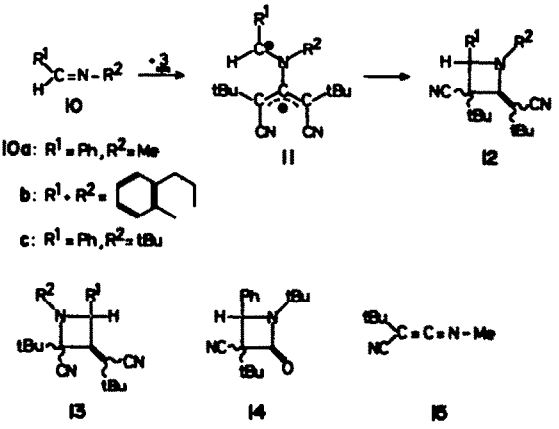
Interestingly, in an attempt to synthesize the allene 8 from the carboxylic acid 6 and the combination of triphenylphosphine and tetrachloromethane, the allene 8 could not be detected, but the diene 9 was obtained. It seems probable that 8 is an intermediate, but under the reaction conditions a 1,3 H shift appears to be favoured in 8 (Scheme 2).



Scheme 2.

Cycloadditions of the allene 3 *to azomethines* **10**. *On* heating or on prolonged standing at room temperature without a solvent, the allene 3 and the azomethines **10a** or **b** yield 1:1 adducts. In agreement with the fixed Z-geometry of the C=N moiety, 3,4-dihydroisoquinoline (**10b**) proved to be more reactive than the conformationally flexible **10a**. While the reaction of 3 and **10a** furnishes a single stereoisomer, the 1:1 adduct **12a** from 3 and **10a** was found to be a mixture of stereoisomers, which could be separated by chromatography.

Formulae **11**–**13** represent possible structures of the 1:1 adducts isolated (Scheme 3). The dipolar formula **11** is rejected because of the observed magnetic nonequivalence of the t-Bu groups and because of the relative insensitivity of the products to hydrolysis. Arguments against **13** and for the regioisomeric **12**, the result of ring closure in **11**, come from ^{1}H NMR and MS data. For the isomers from 3 and **10a**, the ^{1}H chemical shifts of the methine protons and of the t-Bu resonances at higher field, as given in the Experimental, show striking similarity to the corresponding peaks in the spectra of the stereoisomeric β-lactames **14** resulting from cycloaddition of the keten 1 to **10c**.[13] This suggests that the manner in which 3 adds to **10a** parallels that of 1 and the structure **12** can be inferred for the cycloadducts. At the same time, the ^{1}H NMR data indicate that, as is

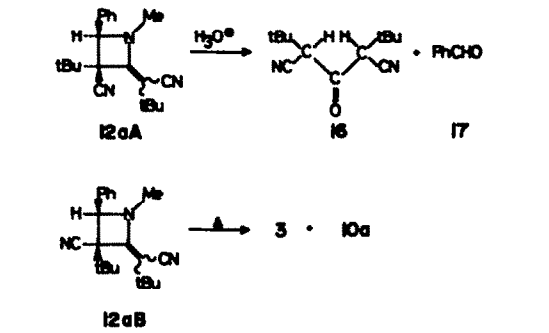


Scheme 3.

the case with 14, the site of stereoisomerism is the heterocyclic ring, where *cis* or *trans* arrangements of the t-Bu group with respect to the phenyl residue R^1 are conceivable. For the sterically more favourable *trans* isomer 12aA, the resonance of the t-Bu group on C-3 should appear at lower field than for 12aB. On this basis, the structure 12aA is assigned to the preponderant isomer. In agreement with this assignment is the considerable broadening of the high-field t-Bu resonance in the ^{1}H NMR spectrum of the other isomer 12aB which on cooling indicated hindered internal rotation around the C-3–t-Bu bond caused by steric congestion with the phenyl residue. This temperature dependence in the ^{1}H NMR spectrum of 12aB would not be consistent with the alternate structure 13.

Additional support for the structure 12 of the cycloadducts is provided by the fragmentation pattern of 12aA in the mass spectrum. Here characteristic fragment ions are observed at *m/e* 136 (31%) and 121 (100%). The peak at *m/e* 136 obviously corresponds to the ketenimine 15, which is generated from 12a by cycloreversion of the molecular ion contrary to the mode of formation, and the subsequent elimination of a Me radical from 15^+ leading to the fragment at *m/e* 121.

Finally, the structural assignment of the cycloadducts 12 is consistent with the proposed electrophilic nature of the central C atom in electron-deficient allenes,[6] from which attack of the nucleophilic nitrogen in 10 to give 12 via 11 can be deduced. Thus the cycloaddition of 3 to 10 is formally analogous to the pertinent reaction of the keten 1. However, the allene 3 is less reactive than 1 and gives no indication for the formation of 2:1[13] or 3:1[9] cycloadducts.



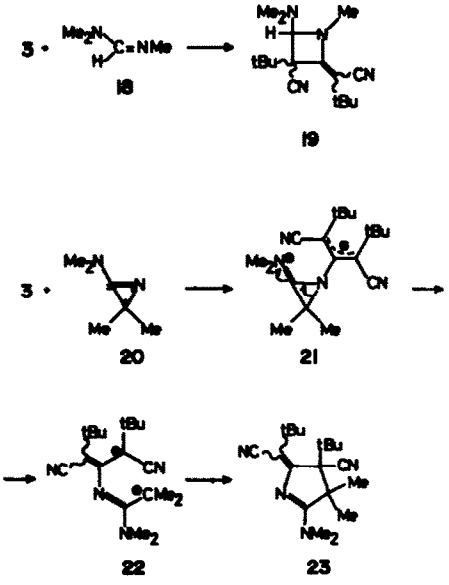
Scheme 4.

Chemical proofs of the structure 12 are rendered difficult by the pronounced tendency of the cycloadducts to give cycloreversion. Thus on heating (18 hr, 120°) in *o*-dichlorobenzene, the strained stereoisomer 12aB yields the starting materials 3 and 10a (Scheme 4); renewed cycloaddition was not observed as it appears to be slow in the dilute solution. In accord with the more favourable steric interactions, the alternate stereoisomer 12aA proved to be stable under the reaction conditions. However, an attempt to hydrolyse 12aA led to the ketone 16, which is a known product of hydrolysis of the heterocycle 2[10] and may also result from the allene 3. Complementary to 16, benzaldehyde (17) was found as the result of hydrolysis of the azomethine 10a.

Cycloadditions of 3 *to amidines.* The reaction of 3 and the formamidine 18 affords a 1:1 adduct to which the structure 19 is assigned in analogy with 12. Stereoisomers could not be detected in 19. Already on standing in solution at room temperature, the 4-amino-2-alkylidene azetidine 19 cleaves to give the original starting materials 3 and 18.

A different cycloaddition mode is observed in the reaction of 3 with the cyclic amidine 20. Here in the first step the dipole 21 can be expected to be formed, but it does not cyclize via C-3 of the original azirine. Instead, cleavage of the original 1,2 bond occurs with the possible intermediacy of 22, and the 1-pyrroline 23 is obtained (Scheme 5). The structural assignment of the (3+2) cycloadduct 23 follows from the comparison of the spectral data with those of similar compounds derived from 3-dialkylamino-2H-azairines.[14] The pyrroline 23 can be separated into two stereoisomers. Undoubtedly, the exocyclic C=C bond is the site of stereoisomerism, but configurational assignments are not possible.

The behaviour of 3 in the reaction with 20 is in apparent contrast to the cycloaddition of the related keten 1 to 20, which occurs across the 1,3 bond of the azirine with subsequent ring-opening of the bicyclic species formed.[15] However, there is unambiguous evidence for cleavage of the 1,2 bond of 20 in the reaction with other ketens.[14]



Scheme 5.

EXPERIMENTAL

M. ps were determined with a Leitz hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian T 60, EM 360 or NV 14 instrument, and ^{13}C NMR spectra with a Bruker WP 60 instrument. $CDCl_3$ was used as solvent unless otherwise noted. IR spectra were determined with the Perkin Elmer spectrometer 297 in KBr discs unless otherwise noted. The mass spectrum was recorded on a Varian MAT CH 7 spectrometer. Preparative tlc was carried out with silica gel PF 254 as purchased from Merck, Darmstadt.

2-Cyano-3,3-dimethylbutyryl chloride (5). The acid 4[11] was treated with thionyl chloride in the usual way. Immediate work-up by fractionate distillation gave a 72% yield of 5; b.p. 53–54°/3 Torr. NMR (CCl_4) 1.22 (9H, S, tBu), 3.68 (1H, s, CHCN). IR data as in *Ref.*[10]

Allene 3 from chloride 5. The acyl chloride 5 was dissolved in toluene and the equimolar quantity of NEt_3 added at 0°. Work-up followed the procedure of Moore and Duncan.[10]

Treatment of 4 or 6 with triphenylphosphine/CCl_4. The acid 4 or 6 (0.085 mol) and triphenyl phosphine (4.46 g, 0.17 mol) were dissolved in a mixture of CCl_4 (13 g, 0.085 mol) and 150 ml toluene. The resulting soln was stirred at room temp. for 3 days and fractionated *in vacuo*. Starting from 4, 1.20 g (9%) of 5 and 3.48 g (41%) of 3, b.p. 86–87°/0.2 Torr, were isolated. The reaction of 6 gave a complex mixture, in which the allene 8 could not be detected. Distillation *in vacuo*, followed by ptlc of the fraction boiling at *ca.* 80°/0.3 Torr using EtOAc–petrol ether (v/v, 1:4) gave *2,6-dimethyl-2,4-heptadiene-3,5-dicarbonitrile* (9), yield: 0.15 g (2%); m.p. 55–56°; IR ν 2240, 2220 cm^{-1} (C≡N), 1640, 1580 cm^{-1} (C=C); ^{1}H NMR δ 1.24 (6H, d, J = 7 Hz, iPr-CH_3), 2.08 and 2.28 (each 3H, s, =C–CH_3), 2.6 (1H, m, iPr-CH), 6.84 (1H, s, =CH). (Found: C, 76.00; H, 8.09; N, 15.98. Calc. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08%).

General procedure for the cycloaddition of 3 to C=N compounds. Equimolar quantities of the components were mixed and stirred at a set temp. for the time indicated below. The products were obtained by recrystallisation of the crude mixture or by ptlc. The following cycloadducts were prepared (reaction temp.; time; isolation procedure):

3 - t - Butyl - 2 - (1 - cyano - 2,2 - dimethylpropylidene) - 1 - methyl - c - 4 - phenylazetidine - r - 3 - carbonitrile (12aA). (120°; 80 hr; crystallisation from EtOAc–petrol ether, an additional crop was obtained by ptlc using EtOAc–petrol ether–dichloromethane (v/v, 1:4:1)), yield 60%; m.p. 203–206°; IR ν 2240 and 2180 cm^{-1} (C≡N), 1630 cm^{-1} (C=C); ^{1}H NMR δ 1.28 and 1.33 (each 9H, s, tBu), 2.95 (3H, s, NMe), 4.60 (1H, s, CH), 7.2–7.6 (5H, m, Ph); on cooling to −99° (solvent CH_2Cl_2–CS_2, v/v, 1:1) both tBu signals are similarly broadened; ^{13}C NMR δ 155.9 (C-2 of the ring), 134.0, 129.3, 128.8, and 127.2 (Ar), 120.1 and 115.2 (C≡N), 87.2 (=C–CN), 69.5 (CH), 58.2 (C-3 of the ring), 38.4 and 31.1 (Ç–Me), 36.5 (N–Me), 31.9 and 26.4 (tBu–CH_3); MS *m/e* 321 (M$^+$, 16%), 306 (M–Me, 33%), 278 (306–C_2H_4, 13%), 265 (M–C_4H_8, 13%), 250 (265–Me, 36%), 136 (15, 31%), 121 (136–Me, 100%), 119 (10a, 11%), 118 (119–H, 38%). (Found: C, 78.58; H, 8.56; N, 13.01. Calc. for $C_{12}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07%).

3 - t - Butyl - 2 - (1 - cyano - 2,2 - dimethylpropylidene) - 1 - methyl - t - 4 - phenylazetidine - r - 3 - carbonitrile (12aB). (120°; 80 hr; ptlc of the mother liquor from the crystallization of 12aA); yield 10%; m.p. 166–168°; IR ν 2230 and 2180 cm^{-1} (C≡N), 1620 cm^{-1} (C=C); ^{1}H NMR δ 1.03 and 1.38 (each 9H, s, tBu), 2.80 (3H, s, NMe), 5.07 (1H, s, CH), 7.35 (5H, s, Ph), on cooling to −95° (solvent CH_2Cl_2–CS_2, v/v, 1:1) the peak at 1.03 is considerably broadened; ^{13}C NMR δ 158.8 (C-2 of the ring), 133.0, 129.2, and 128.7 (Ar), 119.1 and 118.0 (C≡N), 94.5 (=Ç–CN), 73.4 (CH), 54.9 (C-3 of the ring), 40.6, 39.1, and 32.7 (Ç–CH_3 and N–Me), 31.5 and 27.7 (tBu–CH_3). (Found: C, 78.53; H, 8.80; N, 12.96. Calc. for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07%).

1 - t - Butyl - 2 - (1 - cyano - 2,2 - dimethylpropylidene) - 1,4,5,9b - tetrahydroazeto[2,1-a] isoquinoline - 1 - carbonitrile (12b). (20°; 24 hr, in toluene; crystallisation from EtOAc–petrol ether); yield 67%; m.p. 204–205°; IR ν 2230 and 2180 cm^{-1} (C≡N), 1610 cm^{-1} (C=C); ^{1}H NMR δ 1.33 and 1.38 (each 9H, s, tBu), 4.91 (1H, s, CH), 7.2–7.5 (4H, m, Ar–H); ^{13}C NMR δ 155.9 (C-2), 134.6, 131.4, 129.5, 128.0, and 127.2 (Ar), 119.0 and 114.6 (C≡N); 93.2 (=C–CN), 61.7 (C-9b), 58.0 (C-1), 45.4 (C-4), 38.0 and 32.0 (Ç–CH_3), 30.0 and 26.6 (tBu–CH_3), 27.1 (C-5). (Found: C, 79.22; H, 8.43; N, 12.59. Calc. for $C_{22}H_2N_3$: C, 79.24; H, 8.16; N, 12.60%).

1 - t - Butyl - 2 - (1 - cyano - 2,2 - dimethylpropylidene) - 4 - dimethylamino - 1 - methylazetidine - 3 - carbonitrile (19). (20°; 24 hr; crystallization from petrol ether); yield 58%, m.p. 77–81°; IR ν 2240 and 2180 cm^{-1} (C≡N), 1620 cm^{-1} (C=C); ^{1}H NMR δ 1.23 and 1.33 (each 9H, s, tBu), 2.67 (6H, s, NMe_2), 3.07 (3H, s, NMe), 4.27 (1H, s, CH). (Found: C, 70.50; H, 10.09; N, 19.31. Calc. for $C_{17}H_{28}N_4$: C, 70.79; H, 9.78; N, 19.42%).

4 - t - Butyl - 5 - (1 - cyano - 2,2 - dimethylpropylidene) - 2 - dimethylamino - 3,3 - dimethyl - 1 - pyrroline - 4 - carbonitrile (23). (70°; 6 hr; ptlc using EtOAc–petrol ether–CH_2Cl_2 (v/v, 2:4:1)). Preponderating isomer: yield 49%; m.p. 167–168°; IR ν 2230 and 2180 cm^{-1} (C≡N), 1620 cm^{-1} (C=C), 1540 cm^{-1} (C=N); ^{1}H NMR δ 1.18 and 1.33 (each 9H, s, tBu), 1.38 and 1.58 (each 3H, s, Me on C-3), 3.12 (6H, s, NMe_2), $\Delta G^{\neq}$ of hindered internal rotation around the C–NMe_2 bond 52.1 kJ/mol (T_c-49°, $\Delta\nu$ 1.5 Hz); ^{13}C NMR δ 173.6 (C=N), 160.5 (C-5), 120.0 and 117.9 (C≡N), 103.1 (=Ç–CN), 68.4 and 54.4 (C-3, C-4), 40.3 and 34.2 (Ç–CH_3 of tBu), 40.1 (NMe_2), 29.8 and 28.7 (tBu–CH_3), 22.4 (broad, Me on C-3). (Found: C, 73.01; H, 10.01; N, 17.75. Calc. for $C_{19}H_{30}N_4$: C, 72.57; H, 9.62; N, 17.82%). Other isomer: yield 39%; m.p. 147–149°; IR ν 2230 and 2190 cm^{-1} (C≡N), 1610 cm^{-1} (C=C), 1530 cm^{-1} (C=N); ^{1}H NMR δ 1.18 (9H, s, tBu), 1.45 (12H, s, tBu and one Me on C-3), 1.56 (3H, s, Me on C-3), 3.09 (6H, s, NMe_2), $\Delta G^{\neq}$ of hindered internal rotation around the C–NMe_2 bond 55.0 kJ/mol (T_c-35°, $\Delta\nu$ 2 Hz); ^{13}C NMR δ 171.7 (C=N), 162.1 (C-5), 120.7 and 120.3 (C≡N), 108.9 (=Ç–CN), 66.9 and 55.8 (C-3, C-4), 39.9 (NMe_2 and possibly one Ç–CH_3 of tBu), 34.3 (Ç–CH_3 of tBu), 32.5 and 29.8 (tBu–CH_3), 27.9, 22.2 (Me on C-3). (Found: C, 72.58; H, 10.00; N, 17.77. Calc. for $C_{19}H_{30}N_4$; C, 72.57; H, 9.62; N, 17.82%).

Hydrolysis of 12aA. A mixture of 12aA (0.5 mmol), 2 N HCl (5 ml), and dioxane (5 ml) was kept at 100° for 4 days. After neutralization with $NaHCO_3$ and extraction with ether an oil was obtained, which according to IR and NMR spectroscopic evidence consisted of the ketone 16[10] and benzaldehyde (17).

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