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CONJUGATIVE CYCLOADDITION OF N-CHLOROSULFONYL ISOCYANATE ACROSS VINYLCYCLOPROPANE SYSTEM. A NEW PATHWAY TOWARDS MACRO-HETEROCYCLES

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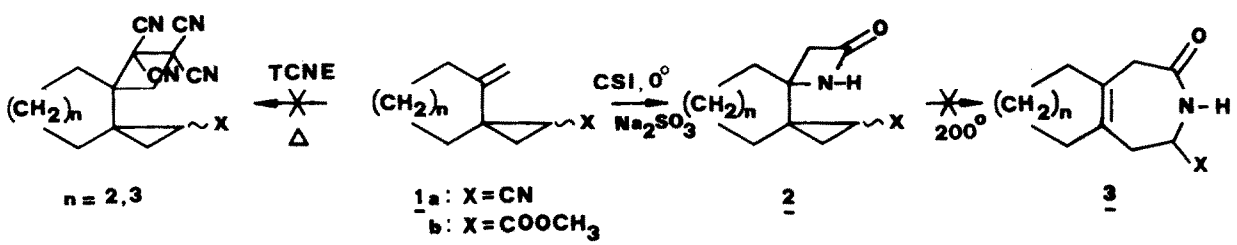
Summary. *trans-* -*Iso*propenyl-4-methylene-*spiro*[2.x]alkanes (4a and 4b) react at 0°C with CSI to give as major products the *trans* bicyclic cycloazanondienones (12a-12b) and as the minor products bicyclodihydro-azepinones (11a and 11b), and the respective *cis* isomer of bicyclic cycloazanondienones (13a and 13b).

Our studies[1] indicated that the electron donor capacity of the σ,π-electron system in 4-methylene-*spiro*[2.x]alkanes (1) is sensitive to substitution effects both in displacement reactions with $Fe(CO)_5$ and in [2+2]cycloadditions with electron-deficient olefins. The inclusion of substituents of high electron demand such as CN or $COOCH_3$ into the small ring in (1) was demonstrated to preclude entirely their reaction with tetracyanoethylene (TCNE).[2] By contrast, N-chlorosulfonyl isocyanate (CSI) cycloadded to the vinylic group in (1) to yield the *spiro*-β-lactam (2) which showed no tendency to add in turn to the *spiro*-cyclopropane to form the dihydroazepinone (3).



Replacement of the nitrile for an isopropenyl group in (1) was shown to impart considerably greater conjugative delocalization to the multi-π,σ-electron system in (4). This was inferred from the facile formation of nine-membered ring adducts on reaction with TCNE,[3] and of eight-membered ring dienones from photolysis of (4a-b) in presence of $Fe(CO)_5$.[4]

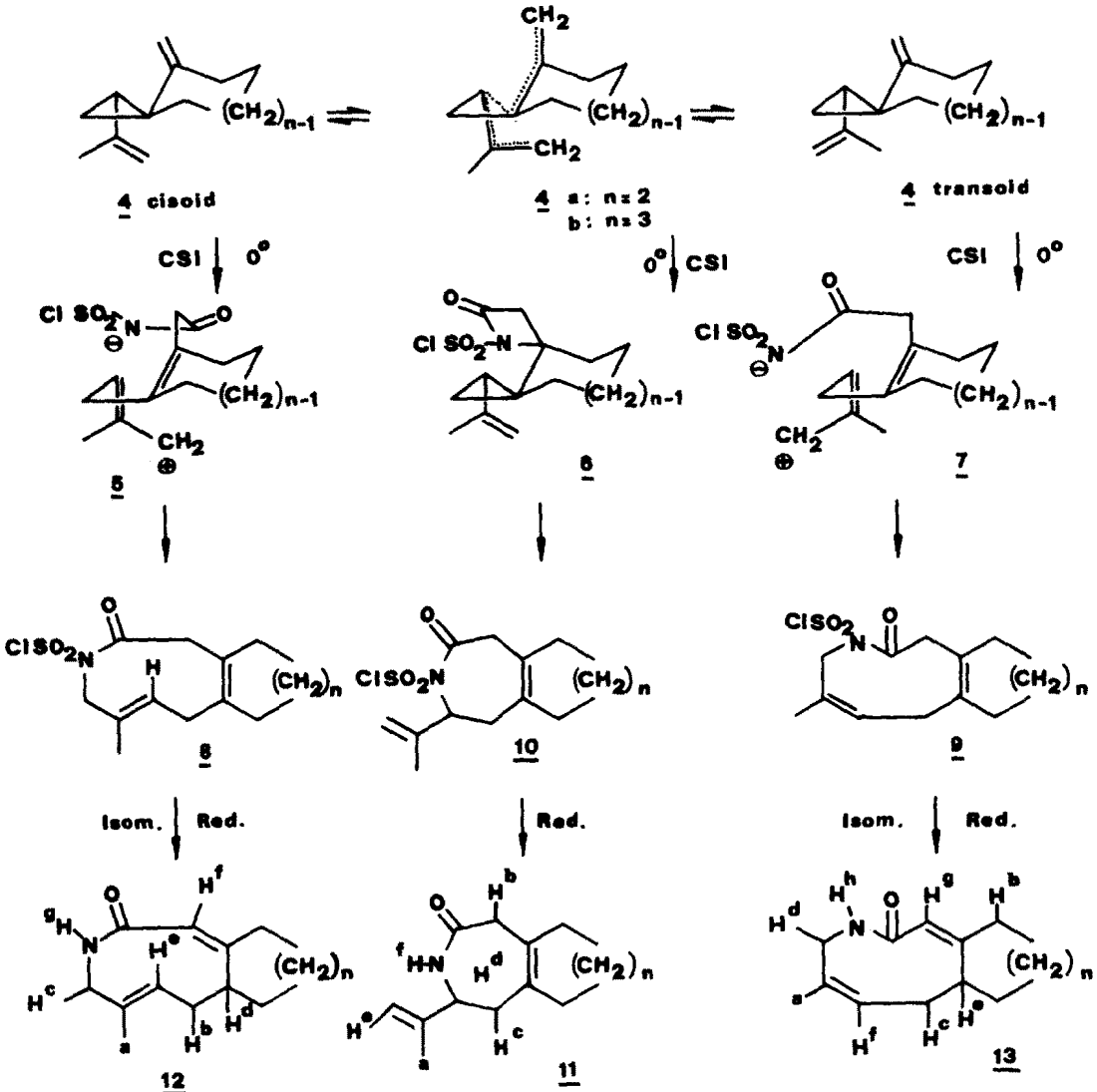
Earlier, Paquette, Kirschner and Malpass[4] have shown that the cyclopropane-containing unsaturated polycyclic system of bullvalene adds CSI at 0° to yield tricyclic adducts containing nine-membered ring lactam (17%), in addition to nine-membered ring lactone (31%) and (19%) β-lactam.

The goal of this study was to realize modes of cycloaddition of CSI to *trans*-1-isopropenyl *spiro*[2.x]alkanes and gain synthetic entry to novel azamacrocycles of potential medicinal interest.

trans-1-*Iso*propenyl-4-methylene-*spiro*[2.x]alkane (4a and 4b) were exposed to the action of small excess of CSI in dry ether at 0°C and the progress of the reaction monitored by ir spectroscopy. The formation of the respective *spiro*-β-lactams (6a and 6b) [ir (CH_2Cl_2): 1820s, 1750s, 1580m, 1200-1180s cm^{-1}] was noted immediately. We did not attempt to isolate the latter because of their tendency to add to the *spiro*-cyclopropane and/or to the *spiro*-cyclopropylethylene to form the respective seven- (10) and nine-membered ring lactams (8 and 9) as the temperature elevated. After reduction with Na_2SO_3 and separation by either fractional crystallization, TLC or gas chromatography, we succeeded to isolate from the above reaction with (4a) (68%) three isomeric 1:1-adducts (11a):(12a):(13a)in 15:67:18 ratio and in parallel from (4b) (74%) the similar adducts:(11b):(12b):(13b) in a ratio of 11:74:15, respectively.

The dihydroazepinone structure of (11a) followed from its (i) elementary analysis as a $C_{13}H_{19}ON$ product; (ii) its ir (NaCl) bands at 3350m (N-H), 1735s (CONH), 1650m (C=C), 900m (C=C) cm^{-1}; (iii) its ^1H-nmr (60 MHz, $CDCl_3$) spectrum lacking cyclopropane signals and exhibiting τ 8.14 (3H, s, H^a), 7.91-7.12 (2H, m, H^c), 7.14-6.92 (2H, m, H^b), 6.08 (1H, bd, J=14 Hz, H^d), 5.04 (1H, s, H^e), 4.92 (1H, s, H^e), 2.75 (1H, finely split s, H^f); (iv) its mass spectrum exhibited m/e 206 (M+1, 8%), 108 (C_8H_{12}, 100%).[6]

The major nine-membered-ring product (12a) was higher melting (m.p. 191-192°C) and of lower retention time (R_t= 37 min.) than the minor product (13a) (m.p. 188-189°C; R_t= 45 min., 20% Carbowax 20M, 200°C, fl. 80 ml/min.).


4 cisoid
4 a: n=2
b: n=3
4 transoid
CSI
0°
5
6
7
8
10
9
Isom.
Red.
12
11
13

The *trans* isomer (12a) had (i) ir (KBr): 3200m (NH), 3080m, 1660s (CONH), 1630m (C=C), 900s (C=C); (ii) nmr (100 MHz, $CDCl_3$: lacking cyclopropane signals, 8.98-7.58 (8H, m), 8.18 (3H, s, H^a), 7.32 (2H, d, J=15Hz, H^b), 6.48 (2H, bd, J=16Hz, H^c), 5.79 (1H, q, J=5Hz, H^d), 5.04 (1H, d, J=3Hz, H^e), 4.02 (1H, bs, H^f), 3.91 (1H, bs, H^g); (iii) uv (ether): 200 nm (ε=1000), 236 (ε=1200), 256 (ε=400); (iv) ms (70 ev): m/e 206 (M^++H, 20%), 205 (M^+, 43%), 93 (100%).[6]

The pertinent data for the *cis* isomer (13a) was : (i) ir (KBr): 3460m, 3200s (NH), 1650s (CONH), 1620m (C=C), 900m, 860m (C=C); (ii) nmr (100 MHz, $CDCl_3$): 8.88-7.75 (m, 6H), 8.20 (3H, s, H^a), 7.59 (2H, d, J=12Hz, H^b), 6.98 (2H, dd, J=15Hz, 5Hz, H^c), 6.49 (2H, bd, J=12Hz, H^d), 5.95 (1H, d, J=12Hz, H^e), 5.44 (1H, dd, J=15Hz, 10Hz, H^f), 4.46 (1H, t, J=9Hz, H^g), 3.95 (1H, bs, H^h); (iii) uv (ether): 200 nm (ε=1000), 236 nm (ε=8000); (iv) ms (70 ev): 205 (M^+, 22%) 97 97 (100%).[6]

The emergence of (11), (12) and (13) from the reaction with CSI can be rationalized in terms of *cisoid - transoid* conformer of (4) which experience an electrophilic attack, preferably at the methylene rather than at the isopropenyl carbon, to form the zwitter-ions (5) and (7) which collapse into (8) and (9). Reductive removal of the chlorosulfonyl group from (8) and (9) was accompanied with double-bond migration, providing the thermodynamically more stable α,β-unsaturated lactams (12) and (13).

Thermodynamically, the *spiro*-β-lactams (6a-6b) appear to be unstable, exhibiting tendency to add to the *spiro*-cyclopropane to form first the respective dihydroazepinones (10a), (10b) and then their isomers (11a) and (11b). The *spiro*-β-lactams of the parent species 4-methylene *spiro*[2.x]alkanes, by contrast could not be detected, yielding the corresponding dihydroazepinones even at -70°.[7]

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