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Mendeleev Commun., 2006, **16(5)**, 276–278
Mendeleev Communications

3-Methylcyclopropene-3-carbonitrile as a new enophile of the Alder-ene reaction

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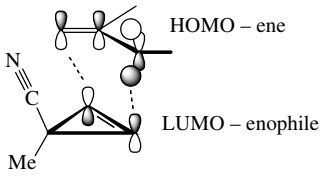
DOI: 10.1070/MC2006v016n05ABEH002328

By the reactions of 3-methylcyclopropene-3-carbonitrile with methylenecyclohexane, α-methylstyrene and β-pinene products of their cyclopropanation have been obtained, the formation of the latter proceeding by the Alder-ene addition scheme. A DFT study of the reaction mechanism shows that most favourable are *exo* transition states with *syn* configuration of the CN group and the ene moiety.

3,3-Disubstituted cyclopropenes constitute a family of cycloolefines, ring strain of which creates their high reactivity in different addition reactions, and the complete substitution of hydrogen of tetragonal carbon for functional groups makes rather thermally stable.[1,2] Reactions of cycloaddition, the reaction of Diels–Alder to the utmost, are quite typical of 3,3-disubstituted cyclopropenes and are of substantial synthetic interest as a way of cyclopropanation of organic compounds.[3,4] 3-Methylcyclopropene-3-carbonitrile (MCPC) is standing aside in the whole series of 3,3-disubstituted cyclopropenes due to its stability (it can be distilled and stored under ambient conditions), and due to its activity and stereoselectivity in the Diels–Alder reactions of nucleophilic addition and cycloaddition.[5–7]

The similarity of cyclization mechanisms of the Diels–Alder and Alder-ene addition[8] allowed us to make an assumption of the interaction of MCPC as an enophile in the Alder-ene reaction, taking into account the efficient electron-acceptor influence of nitrile function on π-olefin bond of the cycle, confirmed by photoelectron spectroscopy (PES) data.[9] We studied the interaction of MCPC with methylenecyclohexane **1**, α-methylstyrene **2** and β-pinene **3**, since the participation of ene systems with *exo*-methylene new olefin fragment of the general structure $RCH_2(R')C{=}CH_2$ (Scheme 1) in the Alder-ene reaction is preferable.[7]

Reactions of MCPC with olefins **1**–**3** were carried out in sealed ampoules without solvent at an equimolar ratio of reagents and were complete in 2 h at 100–120 °C. Reaction mixtures were analysed by chromatography–mass spectrometry, and the products were separated by column chromatography on silica gel by petroleum benzene. Structures of the compounds were defined



Scheme 1

on the basis of IR and NMR spectroscopy and mass spectrometry and confirmed by elemental analyses.† In all of the reactions, the formation of 1:1 adducts as the main products has been established with good yields (Scheme 2).‡

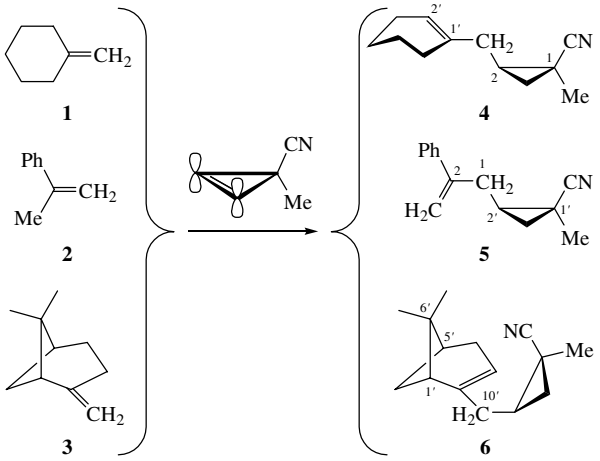
The interaction of MCPC with olefin **1** gave an adduct with *m*/*z* 175, in IR spectra of which there is a characteristic absorption band of nitrile function; and in its ^{1}H NMR spectrum the signals of protons are present: three-membered cycle, single methyl group, four methylene groups, methylene link connecting cyclopropane and cyclohexane fragments, proton at the olefin bond.§ All these data unambiguously allow us to identify the product of the reaction of MCPC with olefin **1** as compound **4**.

The product of the reaction of MCPC with olefin **2** had *m*/*z* 197, in its IR spectra there was a characteristic band of the nitrile function; and in its ^{1}H NMR spectrum there were signals of protons: at three-carbon cycle, methyl group, methyl saturated and methylene olefin fragments, protons of benzene.§ On the basis of these data, we conclude that the product of reaction of MCPC with olefin **2** is compound **5**.

By the interaction of MCPC with olefin **3**, an adduct with *m*/*z* 215 was obtained, in IR spectra of which there is a characteristic band of the cyano group; and in the ^{1}H NMR spectrum there are signals of protons: three-membered cycle, three methyl groups, three methylene links and proton at the double C=C bond.§ These data allow us to accept structure **6** for the product of the reaction of MCPC with β-pinene.

To determine the configuration of substituents at the cyclopropane ring in products **4**–**6**, we performed a density functional theory (DFT) study on Alder-ene reaction mechanism.¶ Only synchronous pathways were considered. For this reaction, there is the possibility of *endo* and *exo* transition states; for each of them there can be a *syn* or *anti* orientation of nitrile moiety and ene fragment with respect to the cyclopropane ring. Moreover, for β-pinene, the dimethyl-substituted carbon 6′ in the transition state can be either *syn*- or *anti*-oriented to incoming MCPC. We calculated all the possible transition states; relative Gibbs free energies of them are given in Table 1. For all of substrates **1**–**3**, the most favourable transition state is *exo*-TS with the *syn*-nitrile configuration. For pinene, it also requires *anti*-configuration of the dimethyl-substituted carbon (the most favourable TS for it is shown in Figure 1). The energies of Alder-ene reactions corresponding to the most favourable reaction pathways are given in Table 2. One can see that the reactions are highly exoergic with moderate activation barriers. Thus, based on the calculation, we can assign to molecules **4**–**6** configurations shown in Scheme 2.

Therefore, 3-methylcyclopropene-3-carbonitrile has revealed enophile ability in Alder-ene reaction and thereby opens a way to the reactions of cyclopropanation of olefins of disparate structure.



Scheme 2

Table 1 Calculated Gibbs free energies (kcal mol^{-1}) of isomeric transition states of the Alder-ene reaction, relative to the most stable isomeric TS under standard conditions.

Reaction	TS isomer	*exo*, *syn*	*exo*, *anti*	*endo*, *syn*	*endo*, *anti*
1 + MCPC → **4**		0.00	2.78	1.55	4.28
2 + MCPC → **5**		0.00	2.82	4.57	4.72
3 + MCPC → **6**	*syn*-CMe_2	2.47	5.39	9.97	11.30
	anti-CMe_2	0.00	2.78	4.78	6.76

Table 2 Calculated reaction (r) and activation (a) Gibbs free energies, enthalpies and entropies (kcal mol^{-1}) for the Alder-ene addition of MCPC to **1**–**3** corresponding to the most stable transition states (*exo*-, *syn*-) under standard conditions.

Reaction	ΔH_r	ΔS_r	ΔG_r	ΔH_a	ΔS_a	ΔG_a
1 + MCPC → **4**	–44.62	–40.99	–32.40	16.81	–41.81	29.28
2 + MCPC → **5**	–42.21	–43.27	–29.31	12.53	–45.41	26.07
3 + MCPC → **6**	–45.23	–42.57	–32.54	11.15	–45.19	24.62

† Analysis by chromatography–mass spectrometry was carried out with an Agilent 6890N gas chromatograph with a 5973N mass selective detector. IR spectra of samples in liquid paraffin were recorded on a Vektor 22 spectrometer. All NMR experiments were performed in dilute $CDCl_3$ solutions at 30 °C with a Bruker AVANCE-600 spectrometer at 600.000 MHz for ^{1}H and 150.864 MHz for ^{13}C.

‡ MCPC was synthesised by the published method.[5]

Synthesis of compounds **4**–**6** was performed by heating in sealed ampoules the mixture of MCPC (2 mmol) and the appropriate olefin (2.5 mmol) at 120 °C for 2 h.

§ *1-Methyl-1-cyano-2-(methyl-1′-cyclohexenyl)cyclopropane* **4**: oil, yield 75%. IR (*ν*/cm^{-1}): 2240 (ν_{CN}). ^{1}H NMR, *δ*: 0.90–0.93 (dd, 2H, CH_2 of cyclopropane, ^3J 4.5 Hz, ^2J 8.0 Hz), 1.06 (q, 1H, CH of cyclopropane, ^3J 4.5 Hz), 1.36 (s, 3H, Me), 1.54–1.62 (m, 4H, CH_2CH_2 of cyclohexene), 1.97–1.98 (m, 4H, CH_2C=), 2.04 (dd, 1H, CH_2C^2, ^3J 4.3 Hz, ^2J 9.2 Hz), 2.21 (dd, 1H, CH_2C^2, ^3J 4.3 Hz, ^2J 9.2 Hz), 5.51 (sw, 1H, HC=C). Found (%): C, 82.15; H, 9.78; N, 8.06. Calc. for $C_{12}H_{17}N$ (%): C, 82.28; H, 9.71; N, 8.00.

1-(1′-Methyl-1′-cyano-2′-cyclopropyl)-2-phenylprop-2-ene **5**: oil, yield 66%. IR (*ν*/cm^{-1}): 2238 (ν_{CN}). ^{1}H NMR, *δ*: 0.96 (dd, 1H, CH_2 of cyclopropane, ^3J 5.23 Hz, ^2J 8.36 Hz), 1.02 (dd, 1H, CH_2 of cyclopropane, ^3J 3.4 Hz, ^2J 8.34 Hz), 1.18 (q, 1H, CH of cyclopropane, ^3J 7.18 Hz), 1.38 (s, 3H, Me), 2.64 (dd, 1H, CH_2, ^3J 7.16 Hz, ^2J 16.28 Hz), 2.84 (dd, 1H, CH_2, ^3J 6.92 Hz, ^2J 16.25 Hz), 5.24 (s, 1H, C=CH_2), 5.39 (s, 1H, C=CH_2), 7.31 (t, 1H, *p*-H in PhR, ^3J 7.6 Hz), 7.36 (t, 2H, *m*-H in PhR, ^3J 7.45 Hz), 7.44 (d, 2H, *o*-H in PhR, ^3J 7.83 Hz). Found (%): C, 85.32; H, 7.65; N, 7.08. Calc. for $C_{14}H_{15}N$ (%): C, 85.28; H, 7.61; N, 7.11.

1-Methyl-1-cyano-2-(10′-α-pinenyl)cyclopropane **6**: oil, crystallises after two days, yield 88%, mp 39–40 °C. IR (*ν*/cm^{-1}): 2243 (ν_{CN}). ^{1}H NMR, *δ*: 0.81 (s, 3H, 8′-Me), 0.83 (dd, 2H, C^3H_2), 0.96 (q, 1H, C^2H), 1.14 (d, 1H, $C^{7'}H_a$), 1.23 (s, 3H, 9′-Me), 1.29 (s, 3H, 1-Me), 2.00–2.31 (m, 7H, $C^{7'}H_e$, $C^{1'}H$, $C^{5'}H$, $C^{4'}H_2$, $C^{10'}H_2$), 5.28 (sw, 1H, 3′-Me). ^{13}C NMR, *δ*: 10.03 (C^1), 20.65 (C^3), 21.0 (6′-Me), 21.17 (1-Me), 24.13 (C^2), 26.15 (6′-Me), 31.04 ($C^{4'}$), 31.35 ($C^{7'}$), 37.75 ($C^{6'}$), 37.78 ($C^{10'}$), 40.61 ($C^{5'}$), 45.69 ($C^{1'}$), 117.08 ($C^{2'}$), 121.40 (CN), 145.60 ($C^{3'}$). Found (%): C, 83.80; H, 9.75; N, 6.43. Calc. for $C_{15}H_{21}N$ (%): C, 83.72; H, 9.77; N, 6.51.

¶ Density functional theory (DFT) calculations of the Alder-ene addition reaction mechanism were performed using the Priroda[10–12] program. A generalised gradient approximation (GGA) exchange-correlation density functional by Perdew, Burke and Ernzerhoff (PBE)[13] was used with double-zeta-polarized quality, correlation-consistent Gaussian basis set {which was (6*s*,2*p*)/[2*s*,1*p*] contracted for H, and (10*s*,7*p*,3*d*)/[4*s*,3*p*,1*d*] contracted for C, N atoms}.[14] Fine numerical integration grids (1×10^{-7}) and optimization convergence criteria (5×10^{-5}) were used throughout the DFT calculations. Full, unconstrained geometry optimizations were performed; on stationary points obtained, analytical Hessians were calculated. All reactant and product geometries had zero, and all transition states – one negative Hessian eigenvalues, respectively. Calculated harmonic force constants were also used for thermochemistry calculations.

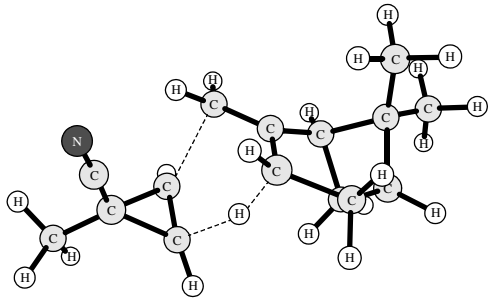


Figure 1 Transition state of Alder-ene reaction of MCPC with **3**, most stable *exo*-TS, *syn*-CN isomer.

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Received: 13th February 2006; Com. 06/2670