Synthesis of cyclopentene derivatives by the cyclooligomerization of isocyanides with substituted benzylidenemalononitriles

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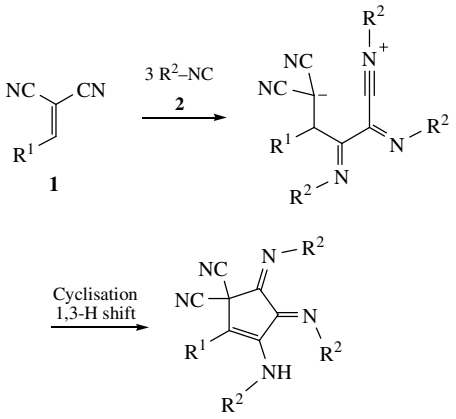
A new reaction of substituted benzylidenemalononitriles with three equivalents of isocyanides leading to the cyclopentene derivatives has been discovered.

The oligomerization of isocyanides accompanied by cyclization is a well-known method for the synthesis of hetero- and carbocyclic products.[1] The initiators of the tandem processes of this type can be Lewis acids,[2] transition metal complexes,[3] tertiary amines,[4] pyridinium salts[5] and compounds containing activated double[6] or triple bonds.[7] Note that, as a rule, an initiator is included in a final structure opening a way to the synthesis of products with different initiator-to-isocyanide ratios. Significant disadvantages of the above methods were low yields (< 40%) and sensitivity to the starting materials. Therefore, new methods should be developed for cyclooligomerization with the participation of isocyanides.

Recently, reactions of activated olefins with isocyanides leading to open-chain products were investigated.[8] It was found that main factors having an influence on the reaction were the structure of an activated olefin, the properties of a solvent and the basicity of the medium. Here, we used activated olefins as initiators for the oligomerization of isocyanides with high selectivity. The synthesis of only four-membered diiminocyclobutanes from two molecules of isocyanide and one molecule of 1,1-dicyano-2,2-ditrifluoromethylethylene was described previously.[6]

We found that the reaction of benzylidenemalononitrile **1a** with three equivalents of *tert*-butyl isocyanide **2a** leads to a single product in a good yield (Scheme 1). Using other olefins **1b–e** and isocyanide **2a** the set of compounds was obtained, structures of which were determined using XRD analysis, NMR spectroscopy and mass spectrometry.† The structure of product **3a** was proved with the help of X-ray analysis,‡ other structures **3b–f** were confirmed by NMR spectroscopy. Thus, ^{1}H NMR spectrum of compound **3c** exhibits the signals of protons typical of three *tert*-butyl and one aromatic groups and yet the presence of an NH group signal confirms the existence of the structure as a single tautomer. The parent mass peak corresponds to the molecular formula of compounds obtained through cooligomerization of three isocyanide molecules and one olefin molecule. X-ray analysis performed for **3a** confirmed the structure of obtained compounds **3** (Figure 1). A distinctive feature of the examined structure is a hydrogen bond between amino and imino functionalities (2.16 Å), which makes this molecule more stable thermodynamically. The double carbon–carbon bond and



3a R^1 = Ph, R^2 = Bu^t
3b R^1 = 4-$NO_2C_6H_4$, R^2 = Bu^t
3c R^1 = 4-ClC_6H_4, R^2 = Bu^t
3d R^1 = 4-FC_6H_4, R^2 = Bu^t
3e R^1 = 3-$MeOC_6H_4$, R^2 = Bu^t
3f R^1 = Ph, R^2 = *c*-C_6H_{11}

Scheme 1 Synthesis of cyclopentene derivatives.

† *General procedure for the synthesis of cyclopentenes* **3a–f**. A solution of benzylidenemalonodinitrile **1a** (0.11 g, 0.7 mmol) and *tert*-butyl isocyanide (0.48 ml, 2.1 mmol) in acetonitrile (0.5 ml) was refluxed for 4 h. The product was collected by filtration and washed with hexane to give **3a** in 57% yield, mp 166–167 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.95 (s, 9H, Bu^t), 1.46 (s, 9H, Bu^t), 1.64 (s, 9H, Bu^t), 5.45 (s, 1H, NH), 7.49–7.54 (m, 5H, Ph). MS, *m*/*z* (%): 403 (21, M$^+$), 404 (6), 347 (100), 320 (20), 235 (25), 208 (27). Found (%): C, 74.71; H, 8.36; N, 17.48. Calc. for $C_{25}H_{33}N_5$ (%): C, 74.41; H, 8.24; N, 17.35.

For **3b**: yield 55%, mp 135–136 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.97 (s, 9H, Bu^t), 1.47 (s, 9H, Bu^t), 1.64 (s, 9H, Bu^t), 5.58 (s, 1H, NH), 7.83 (d, 2H, 3-H, 5-H, *J* 8.9 Hz), 8.39 (d, 2H, 2-H, 6-H, *J* 8.9 Hz). MS, *m*/*z* (%): 448 (31, M$^+$), 449 (9), 393 (25), 392 (100), 365 (27), 57 (100). Found (%): C, 67.19; H, 7.34; N, 18.80. Calc. for $C_{25}H_{32}N_6O_2$ (%): C, 66.94; H, 7.19; N, 18.74.

For **3c**: yield 35%, mp 101–102 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.98 (s, 9H, Bu^t), 1.46 (s, 9H, Bu^t), 1.64 (s, 9H, Bu^t), 5.48 (s, 1H, NH), 7.53–7.59 (m, 4H, Ar). MS, *m*/*z* (%): 437 (1, M$^+$), 381 (5), 269 (28), 242 (19), 77 (23), 57 (100). Found (%): C, 68.76; H, 7.23; N, 15.86. Calc. for $C_{25}H_{32}ClN_5$ (%): C, 68.56; H, 7.36; N, 15.99.

For **3d**: yield 50%, mp 137–138 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.97 (s, 9H, Bu^t), 1.46 (s, 9H, Bu^t), 1.64 (s, 9H, Bu^t), 5.48 (s, 1H, NH), 7.25–7.32 (m, 2H, Ar), 7.52–7.58 (m, 2H, Ar). MS, *m*/*z* (%): 421 (1, M$^+$), 365 (5), 253 (27), 226 (22), 199 (7), 57 (100). Found (%): C, 71.51; H, 7.62; N, 17.15. Calc. for $C_{25}H_{32}FN_5$ (%): C, 71.23; H, 7.65; N, 16.91.

For **3e**: yield 23%, mp 106–107 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.99 (s, 9H, Bu^t), 1.46 (s, 9H, Bu^t), 1.64 (s, 9H, Bu^t), 3.82 (s, 3H, OMe), 5.43 (s, 1H, NH), 7.00–7.12 (m, 3H, Ar), 7.38–7.44 (m, 2H, Ar). MS, *m*/*z* (%): 433 (2, M$^+$), 377 (6), 294 (8), 265 (34), 238 (37), 211 (18), 57 (100). Found (%): C, 71.77; H, 8.12; N, 16.10. Calc. for $C_{26}H_{35}N_5O$ (%): C, 72.02; H, 8.14; N, 16.15.

For **3f**: yield 45%, mp 166–167 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.73–1.81 (m, 30H, *c*-C_6H_{11}), 2.75–2.78 (m, 1H, CHN), 4.06–4.08 (m, 1H, CHN), 4.79–4.80 (m, 1H, CHN), 5.45 (d, 1H, NH, *J* 10.1 Hz), 7.46–7.51 (m, 5H, Ph). MS, *m*/*z* (%): 481 (23, M$^+$), 398 (6), 384 (30), 372 (32), 289 (21), 262 (17), 83 (100). Found (%): C, 77.39; H, 8.28; N, 14.77. Calc. for $C_{31}H_{39}N_5$ (%): C, 77.30; H, 8.16; N, 14.54.

‡ *Crystal data for* **3a**. $C_{25}H_{33}N_5$, M = 403.56, monoclinic, space group $P2_1/n$, a = 10.470(3), b = 10.257(5) and c = 23.741(7) Å, V = 2531.4(16) Å^3, Z = 4, d_{calc} = 1.059 g cm^{-3}, μ = 0.064 mm^{-1}, $F(000)$ = 872. Data collection was performed at 293 K within the θ-range from 1.73 to 25.18°; a total of 4840 (of which 4555 were unique) reflections were collected [R(int) = = 0.0212] and used to refine 271 parameters. The structure was solved with the program SHELXS-97 and refined using SHELXL-97[9] to R_1 = = 0.0716 and wR_2 = 0.1933 [$I > 2\sigma(I)$].

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 616740. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

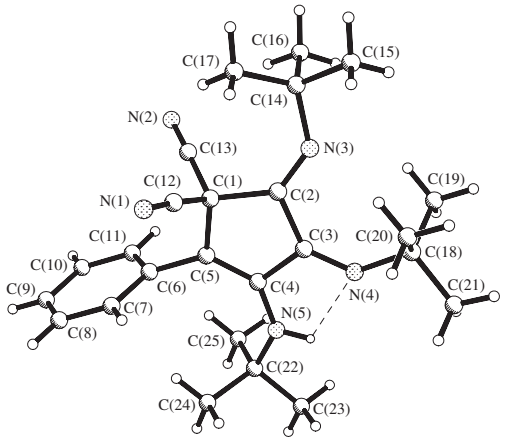


Figure 1 Molecular structure of **3a**.

two imino functions in a five-membered ring system predetermine the almost flat structure of this compound. In that way, the reaction results in the formation of 1:3 adducts, 2-aryl-3-alkylamino-4,5-bis(methylimino)cyclopentene-1,1-dicarbonitriles, and it is an effective method for the synthesis of cyclopentene.

The solvent has an influence on the distribution of reaction products. Thus, we have succeeded in obtaining the target cyclopentenes in polar aprotic solvents like acetonitrile; the use of other non-polar solvents leads to a complex mixture of compounds. We have supposed that a polar solvent can stabilize the subsequently formed zwitterionic intermediates giving cyclic products **3** in moderate yields. In addition, the nature of the aryl fragment has an influence on the results of the synthesis. Thus, the presence of electron-withdrawing substituents leads to an increase in the reaction rate. In contrast, the introduction of electron-donating groups leads to a decrease in the yields of target products. For example, using 2-thienyl as a substituent, we did not succeed in isolating cyclopentene. Note that no cyclic products were detected using one ethoxycarbonyl group instead of a nitrile group. It could be connected with steric hindrances appeared during the cyclization stage. In contrast, the volume of substituents in isocyanides has no influence on proceeding the reaction. The use of commercially available isocyanides **2a**,**b** is given here as an example.

In contrast to our previous investigation,[8] the use of organic bases like triethylamine, pyridine or nicotinic acid ester as a catalyst did not lead to increase in the yields. Three-component variant of this reaction (interaction of isocyanides with aldehydes and malononitrile) was also ineffective.

It is possible to propose the reaction mechanism, which includes subsequent formation of three zwitterionic intermediates, cyclization and 1,3-shift. A polar solvent provides stabilization of zwitterionic intermediates that is the explanation of the high selectivity. Note that four new carbon–carbon bonds are formed during the reaction; moreover, taking into account the easy access to activated olefins, our method allows creating five carbon–carbon bonds at once.

In summary, a new reaction of the cooligomerization of isocyanides with activated olefins has been found. The reaction leads to the derivatives of cyclopentene in good yields.

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New chiral basic heterogeneous catalyst based on Csβ zeolite

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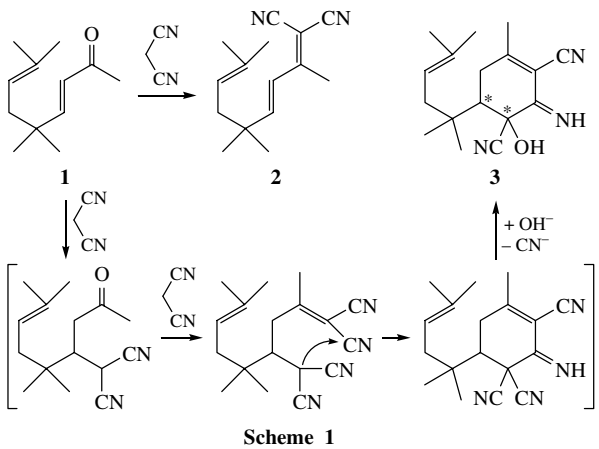
A new basic chiral catalyst Met-Csβ has been synthesised for preparing optically active products of the Michael reaction and tandem transformations by the interaction of starting achiral α,β-unsaturated carbonyl compounds with malononitrile.

The Michael reaction is of importance for forming new carbon–carbon bonds.[1] Special attention has recently been paid to the enantioselective Michael addition.[2] Asymmetric catalysis of the Michael reaction generally employs various homogeneous metallocomplex catalysts,[3] while heterogeneous chiral systems were almost not used for this purpose.[4–6] At the same time, the use of heterogeneous catalysts often permits one to avoid typical disadvantages of homogeneous systems such as difficulties of catalyst separation and recycling.[7]

Previously, we showed that basic zeolite Csβ is an effective catalyst for reactions of α,β-unsaturated carbonyl compounds from the terpenoid series with CH acids.[8,9] The reaction products were the typical products of Michael and Knoevenagel reactions, or tandem transformations, which depended on the structure of the terpenoid. For example, when ketone **1** reacted with malononitrile (Scheme 1) in the presence of zeolite Csβ, the Knoevenagel reaction (product **2**) competed with the Michael



Scheme 1