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A Three-Component Reaction for the Synthesis of 1-Azabicyclo[3.1.0]hexane-3-enes

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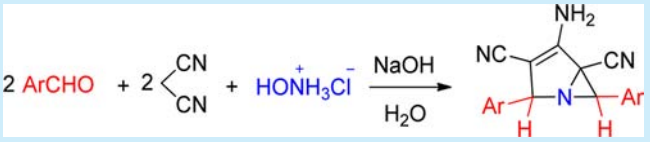
Supporting Information

ABSTRACT: A novel and simple synthesis of 1-azabicyclo[3.1.0]hexane-3-ene derivatives is described. The synthesis is carried out via a simple three-component reaction between aryl aldehydes, malononitrile, and hydroxylamine hydrochloride in water. Eco-friendliness, excellent product yields, short reaction time, inexpensive and readily available starting materials, and interesting reaction and products are the main advantages of this method.



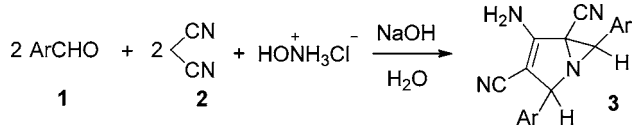
Multicomponent reactions (MCRs) are commonly known and widely used synthetic protocols in the synthesis of many heterocyclic compounds such as pharmaceuticals,[1] fungicides,[2] herbicides,[3] and pesticides. In the past decade, the MCR strategy has gained attention because of its capacity to produce medicinal and other bioactive compounds. The combination of MCR and green chemistry conditions represents a very efficient method from environmental, economic, and synthetic points of view.[4]

Bicyclic nitrogen-containing heterocyclic compounds are of both biological and chemical interest. They are parts of a large number of highly significant biomolecules, such as an effective pathogen killer,[5] and have antitussive and anti-inflammatory effects with analgesic activities.[5a] Some of them are very common in drug molecules possessing various biological activities, such as inhibitors of microsomal prostaglandin E2, antimalarials, antidepressants, antihypertensives, and antihypoglycemics. The fused-ring and bridged-ring moieties, such as 3-azabicyclo[3.1.0]hexane-2-carboxylic acid derivatives, have been found to serve as an effective plant male gametocide and hepatitis C protease inhibitors.[6]

More recently, attention has been focused on this class of compounds. Previously, many methods have been developed for the synthesis of nitrogen-bridged heterocycles.[7] The most common synthetic routes reported for the preparation of nitrogen-bridged heterocycles include (i) Diels–Alder reaction between 2*H*-azirine and Danishefsky's diene yielding 1-azabicyclo[4.1.0]hept-3-ene,[8] (ii) [4 + 2] cycloaddition (aza-Diels–Alder reaction) of imine-substituted dihydropyridines in the presence of $CuCl_2$ and NEt_3,[9] (iii) photocycloaddition reaction of 2,5-diazidohexa-2,4-diene and 2,3-dimethylbuta-1,3-diene to give the corresponding azabicyclo[4.1.0]hept-3-ene,[10] (iv) the reaction of cyclopentadiene and 2*H*-azirine esters leading to an azatricyclo products,[11] (v) reduction of 2-cyanohexahydroindolium salts with $LiAlH_4$ and hydrolysis with NaOH,[12] and (vi) cationic cyclization of an *N*-allyl group onto the α-oxocarbenium ion[13] and nucleophilic attack of PhLi on perfluoro-2,6-dimethyl-1-azacyclohexene to give the corresponding azabicyclo[3.1.0]hexane.[14]

As part of our current studies on the development of efficient and straightforward methods to prepare organic compounds from readily available building blocks,[15] herein we report a simple and efficient method for the synthesis of 1-azabicyclo[3.1.0]hexenes via a unprecedented three-component reaction between aryl aldehydes, malononitrile, and hydroxylamine hydrochloride in water to afford the title compounds **3a–h** in good to excellent yields (Scheme 1 and Table 1).[16]

Scheme 1. Three-Component Synthesis of 1-Azabicyclo[3.1.0]hexenes 3 in Water



The structures of the products were confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and elemental analysis. Finally, single-crystal X-ray analysis of **3b** conclusively confirmed its structure, and by analogy, those of the other isolated products were confirmed too. An ORTEP diagram of **3b** is shown in Figure 1.

Mechanistically, it is reasonable to assume that the first step may involve the condensation of aryl aldehyde **1** and malononitrile **2** to generate 2-benzylidenemalononitrile **4** in situ. Then the addition of one molecule of hydroxylamine

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Table 1. Three-Component Synthesis of 1-Azabicyclo[3.1.0]hexenes 3 in Water

	Ar	yield (%)[a]	melting point (°C)
3a	PhCHO	79	167−169
3b	4-BrPhCHO	90	196−199
3c	4-ClPhCHO	78	203−208
3d	4-NO_2PhCHO	75	177−180
3e	4-MePhCHO	80	173−176
3f	2,4-Cl_2PhCHO	93	190−192
3g	2-ClPhCHO	89	157−159
3h	4-MeOPhCHO	92	184−186

[a]Isolated yields.

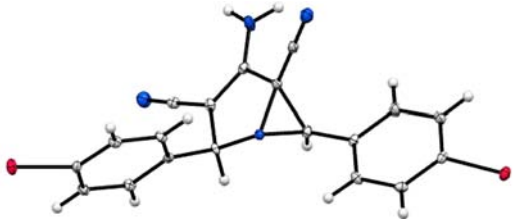
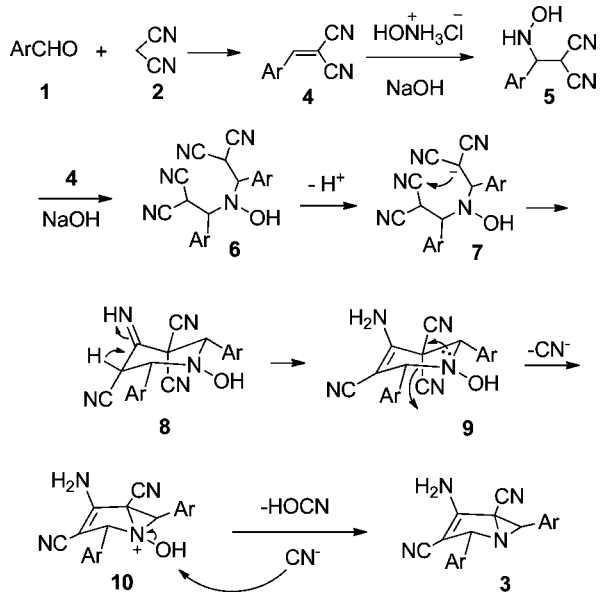


Figure 1. ORTEP diagram of the molecular structure of **3b**.

would lead to the formation of 2-(hydroxyamino)-arylmethylmalononitrile **5**, and addition of another molecule of malononitrile would lead to intermediate **6**. Deprotonation and then cyclization of intermediate **6** would produce 1-hydroxy-4-iminopiperidine **8**, which would undergo a [1,3] H shift to afford enamine **9**. Intramolecular approach of the nitrogen atom in enamine **9** would contribute to the elimination of CN^- (intramolecular S_N2-like reaction). Finally elimination of HOCN or OCN^- in the presence of CN^- would lead to 4-amino-2,6-diaryl-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile **3** (Scheme 2).

All of the chemicals used in this study were purchased from Merck and used without further purification. Melting points were determined with an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu 8400s FT-IR spectrometer using potassium bromide pellets. ^{1}H NMR spectra (300 MHz) were recorded on a Bruker Advance DRX-300 spectrometer. The chemical shifts are reported in parts per million (δ scale) relative to internal TMS, and coupling constants are reported in $CDCl_3$ and DMSO-d_6. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light.

Scheme 2. Possible Mechanism for the Formation of 1-Azabicyclo[3.1.0]hexenes 3



The crystallographic measurements on **3b** were performed on an Xcalibur R κ-geometry automated four-circle diffractometer equipped with a Ruby CCD camera and graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). The data were collected at 90(2) K using an Oxford Cryosystems cooler. Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, data reduction and analysis, and analytical absorption corrections were carried out with Xcalibur R software and CrysAlisPro.[17] The structure was solved by direct methods with SHELXS97[18] and refined by a full-matrix least-squares technique with SHELXL2014[18] with anisotropic thermal parameters for non-H atoms. All H atoms were found in different Fourier maps and were refined isotropically. In the final refinement cycles, the C-bonded H atoms were repositioned in their calculated positions and refined using a riding model, with C−H = 0.95−1.00 Å and with U_{iso}(H) = 1.2U_{eq}(C). Amine H atoms were refined with the N−H bond lengths restrained to 0.880(2) Å and with U_{iso}(H) = 1.2U_{eq}(N), and then they were constrained to ride on their parent atom. Figures were made with the DIAMOND program.[19]

In conclusion, we have developed a practical, simple, and efficient reaction for the preparation of 1-azabicyclo[3.1.0]hex-3-ene derivatives via a three-component reaction method. The method has several advantages, including interesting product structures, high yields of products, easy experimental workup, the use of simple and available starting materials, high atom economy, and eco-friendly and mild reaction conditions without the use of any catalyst or organic solvents. To the best of our knowledge, this is the first report in which highly substituted 1-azabicyclo[3.1.0]hex-3-enes **3** have been synthesized by a novel and simple three-component reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02180.

Synthesis procedure, spectral data, NMR and IR spectra, and X-ray crystallography details (PDF)
Crystallographic data for **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) **Representative experimental procedure and spectral data**: The reaction was carried out by first mixing benzaldehyde (**1a**) (1 mmol), malononitrile (**2**) (1.5 mmol), hydroxylamine hydrochloride (0.5 mmol), and sodium hydroxide (0.5 mmol) in a 5 mL sealed vial in water (1 mL) as a one-pot reaction. Then the reaction mixture was stirred at room temperature for 2 h until generation of the yellow-colored product. TLC monitoring of the reaction mixture clearly indicated the formation of 4-amino-2,6-diphenyl-1-azabicyclo[3.1.0] hex-3-ene-3,5-dicarbonitrile (**3a**) in excellent yield. Afterward, the residue was filtered and recrystallized in ethanol, and then the product **3a** was obtained as light-yellow crystals. **4-Amino-2,6-bis(4-bromophenyl)-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile** (**3b**). White crystals. Yield: 90%. IR (KBr): 3427 (s), 3332 (s), 2244 (s), 2199 (m), 1651 (s), 1604 (m), 1484 (m), 1387 (m), 1012 (m), 814 (s), 492 cm^{-1} (m). ^1H NMR (299.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.34 (s, 1H; CH), 4.91 (s, 1H; CH), 5.10 (br s, 2H; NH_2), 7.28 (d, ^3J(H,H) = 8.7 Hz, 2H, 2CH), 7.30 (d, ^3J(H,H) = 8.7 Hz; 2H), 7.54 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.58 ppm (d, J = 8.4 Hz, 2H; 2CH). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, TMS): δ = 49.28 (CH), 54.12 (C), 71.52 (CH), 72.84 (C), 114.85 and 116.92 (2CN), 121.79 and 122.62 (2C), 129.45, 130.04, 131.86 and 132.25 (8CH), 133.19 (C), 141.46 (C), 155.88 ppm (C-NH_2). Anal. Calcd for $C_{19}H_{12}Br_2N_4$ (456.13): C, 50.03; H, 2.65; Br, 35.04; N, 12.28. Found: C, 50.10; H, 2.68; Br, 35.08; N, 12.33%.

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