A new approach to the synthesis of functionalized bicyclo[3.2.1]octanes

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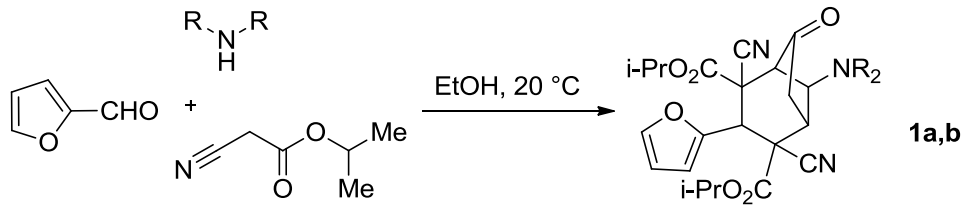
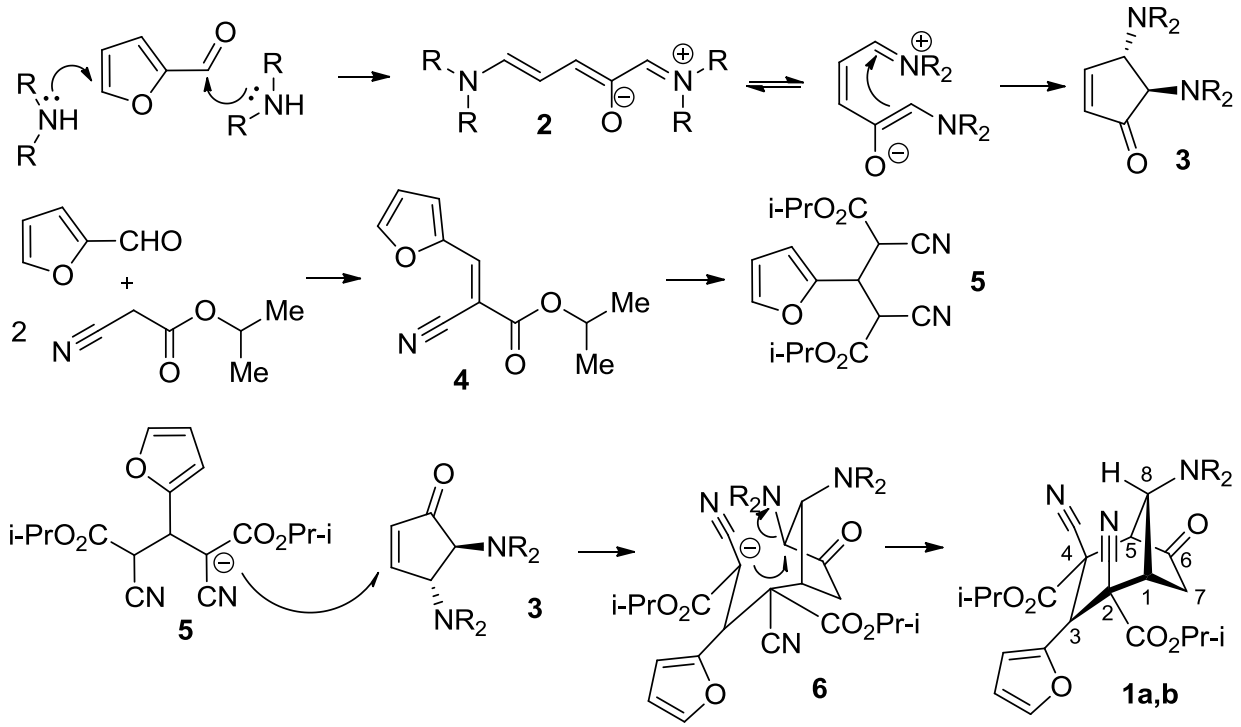
Abstract: The reaction of furfural with secondary amines and isopropyl cyanoacetate leads to the formation of the previously unknown diisopropyl 8-(dialkylamino)-2,4-dicyano-3-(2-furyl)-6-oxobicyclo[3.2.1]octane-2,4-dicarboxylates. The tructure of the products was confirmed by NMR and X-ray analysis.

Keywords: furfural, isopropyl cyanoacetate, Stenhouse salt, Nazarov reaction, carbocyclization, bicyclo[3.2.1]octane.

Recently, a number of papers [1–6] have appeared dealing with the development of various approaches to the synthesis of bicyclo[3.2.1]octanes (for reviews, see [7–9]). First, this bicyclic system is of interest due to the biological activity – thus, inhibitors of dopamine and serotonin transfer [10] were found among bicyclo[3.2.1]octanes. They also can be used in the synthesis of tricyclic terpenoids [11]. Bicyclo[3.2.1]octane motif is the structural core unit of various natural terpene compounds and alkaloids [8]. In continuation of our studies in the chemistry of active methylene nitriles [12–16], we'd like to propose a new approach to the synthesis of bicyclo[3.2.1]octanes based on an elegant cascade reaction between furfural and isopropyl cyanoacetate in the presence of secondary amines. We found that the reaction of furfural with secondary amines and cyanoacetic ester leads to the formation of bicyclooctanes **1a,b** in moderate yields (37–45%).



The proposed mechanism involves the formation of the deprotonated Stenhouse salt **2** from a secondary amine and furfural at first (Scheme 2). It should be noted that when furfural and cyanoacetic ester were put into the reaction simultaneously, the reaction led to the formation of the expected Knoevenagel products, 3-(2-furyl)-2-cyanoacrylates. We suppose that intermediate **2** further undergoes spontaneous Nazarov-type 4π-electrocyclization [17] to give 2,3-diaminocyclopentenones **3**. The formation of **3** from furfural and amines is well known and described in recent literature (e,g, [18-25], see also the review by Piancatelli et al. [26]). When furfural and isopropyl cyanoacetate were added to the reaction mixture, 3-(2-furyl)-2-cyanoacrylate **4** and Michael adduct **5** were formed sequentially. Under basic conditions compound **5** undergo the Michael addition to cyclopentenone **3** followed by carbocyclization of adduct **6**, probably through the nucleophilic substitution of a secondary amine (Scheme 2).



Scheme 2. Probable mechanism of the formation of **1**.

The structure of compounds **1a,b** was confirmed by means of IR and NMR $^{1}H/^{13}C$ data, as well as X-ray diffraction analysis for compound **1a** (Fig. 1).

Conclusion

In summary, we have discovered a new cascade reaction opening a new opportunity for synthesis of functionalized bicyclo[3.2.1]octanes from available reagents under one-pot conditions. The mechanistic details of the reaction, the scope and limitations will be reported elsewhere.

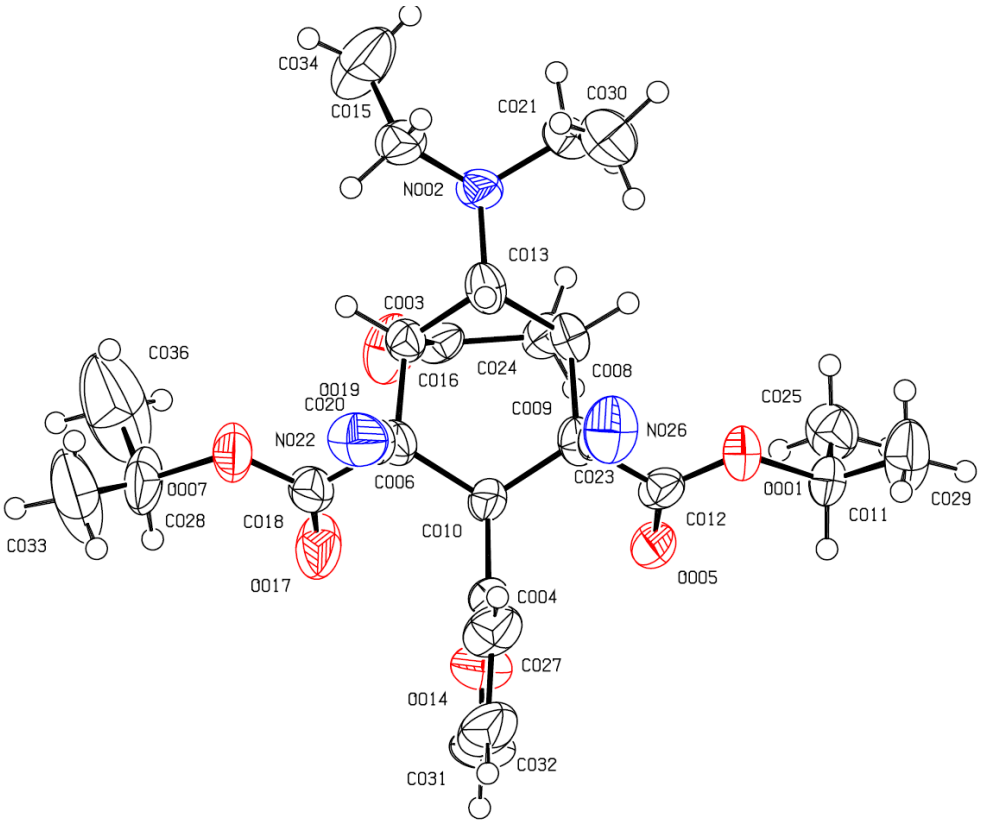
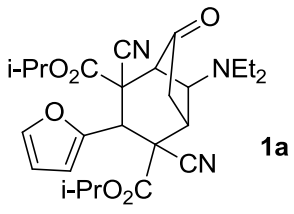


Figure 1. The structure of diisopropyl 2,4-dicyano-8-(diethylamino)-3-(2-furyl)-6-oxobicyclo[3.2.1]octane-2,4-dicarboxylate (**1a**) (X-ray data).

Experimental

IR spectra were recorded on a Varian 3600 FT-IR Excalibur Series spectrometer in KBr pellets. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) in $CDCl_3$. Selected experimental procedure (synthesis of **1a**) is given. Microanalysis was obtained using Carlo Erba 1106 analyzer.

Diisopropyl 2,4-dicyano-8-(diethylamino)-3-(2-furyl)-6-oxobicyclo[3.2.1]octane-2,4-dicarboxylate (1a)



1a

A mixture of 0.83 ml (0.01 mol) of furfural and 0.02 mol of Et_2NH in 96% EtOH (10 mL) was stirred for 2 hours. Then a mixture of 0.83 ml (0.01 mol) of furfural and 2.51 ml (0.02 mol) of isopropyl cyanoacetate was added to the solution under vigorous stirring. The reaction mass was maintained for 24 hours, the precipitated crystals were filtered off.

Beige crystals, yield 37%, mp 154 °C (EtOH). IR, ν, cm^{-1}: 2240 (C≡N), 1750 (C=O), 1654 (CO_2Pr-*i*). NMR ^{1}H (300 MHz, $CDCl_3$), δ, ppm: 1.02 t (6H, 2 $CH_2C\underline{H}_3$, ^3J 7.0 Hz), 1.21-1.30 m (12H, 2 $CH(C\underline{H}_3)_2$), 2.53-2.54 m (2H, H-7), 2.69 q (4H, 2 $C\underline{H}_2CH_3$, ^3J 7.0 Hz), 2.92 br.s (1H, H-8), 3.12-3.14 m (1H, H-1), 3.97 s (1H, H-5), 4.29 s (1H, H-3), 5.01-5.12 m (2H, 2 $C\underline{H}(CH_3)_2$), 6.34 dd (1H, H-4_{furyl}, $^3J_{H(4)-H(3)}$ 3.1 Hz, $^3J_{H(4)-H(5)}$ 1.7 Hz), 6.67 d (1H, H-3_{furyl}, $^3J_{H(4)-H(3)}$ 3.1 Hz), 7.35-7.36 m (1H, H-5_{furyl}). NMR ^{13}C (75 MHz, $CDCl_3$), δ, ppm: 11.1 (2 $CH_2\underline{C}H_3$), 21.14 ($CH(\underline{C}H_3)_2$), 21.18 ($CH(\underline{C}H_3)_2$), 21.23 ($CH(\underline{C}H_3)_2$), 21.27 ($CH(\underline{C}H_3)_2$), 35.6 (C-3), 38.0 (C-1), 42.1 (2 $\underline{C}H_2CH_3$), 42.5 (C-8), 50.4 (C-4 or C-2), 51.8 (C-2 or C-4), 54.5 (C-7), 63.2 (C-5), 72.5 ($\underline{C}H(CH_3)_2$), 72.9 ($\underline{C}H(CH_3)_2$), 110.79 (C-4_{furyl}), 110.81 (C-3_{furyl}), 115.3 (C≡N), 116.2 (C≡N), 142.8 (C-5_{furyl}), 146.6 (C-1_{furyl}), 163.4 ($\underline{C}O_2$Pr-*i*), 165.1 ($\underline{C}O_2$Pr-*i*), 206.9 (C=O). Found, %: C 64.62; H 6.97; N 8.63. $C_{26}H_{33}N_3O_6$. Calculated, %: C 64.58; H 6.88; N 8.69.

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