

Extended Abstract

# A New Approach to the Synthesis of Functionalized Bicyclo[3.2.1]octanes <sup>†</sup>

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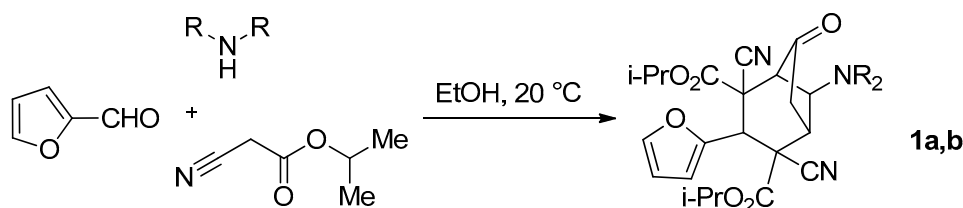
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**Abstract:** The reaction of furfural with secondary amines and isopropyl cyanoacetate leads to the formation of the previously unknown diisopropyl 8-(dialkylamino)-2,4-dicyano-3-(2-furyl)-6-oxobicyclo[3.2.1]octane-2,4-dicarboxylates. The structures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

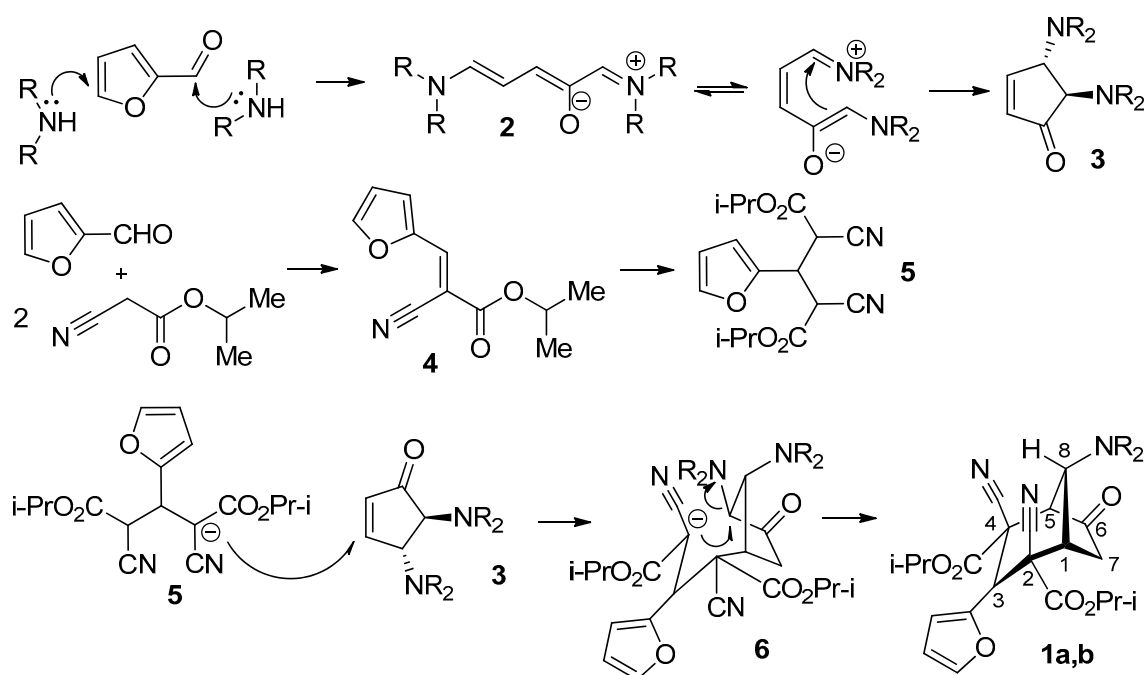
**Keywords:** furfural; isopropyl cyanoacetate; Stenhouse salt; Nazarov reaction; carbocyclization; bicyclo[3.2.1]octane

Recently, a number of papers [1–6] dealing with the development of various approaches to the synthesis of bicyclo[3.2.1]octanes have appeared (for reviews, see [7–9]). First, this bicyclic system is of interest due to its biological activity—inhibitors of dopamine and serotonin transfer [10] were found among bicyclo[3.2.1]octanes. They can also be used in the synthesis of tricyclic terpenoids [11]. The 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 would 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** (Scheme 1) in moderate yields (37%–45%).



**Scheme 1.** Synthesis of compounds **1**.

The proposed mechanism firstly involves the formation of the deprotonated Stenhouse salt **2** from a secondary amine and furfural (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 the intermediate **2** further undergoes spontaneous Nazarov-type  $4\pi$ -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** undergoes 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 structures of compounds **1a,b** were confirmed by means of IR and NMR  $^1\text{H}/^{13}\text{C}$  data, as well as X-ray diffraction analysis for compound **1a** (Figure 1).

## Conclusions

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

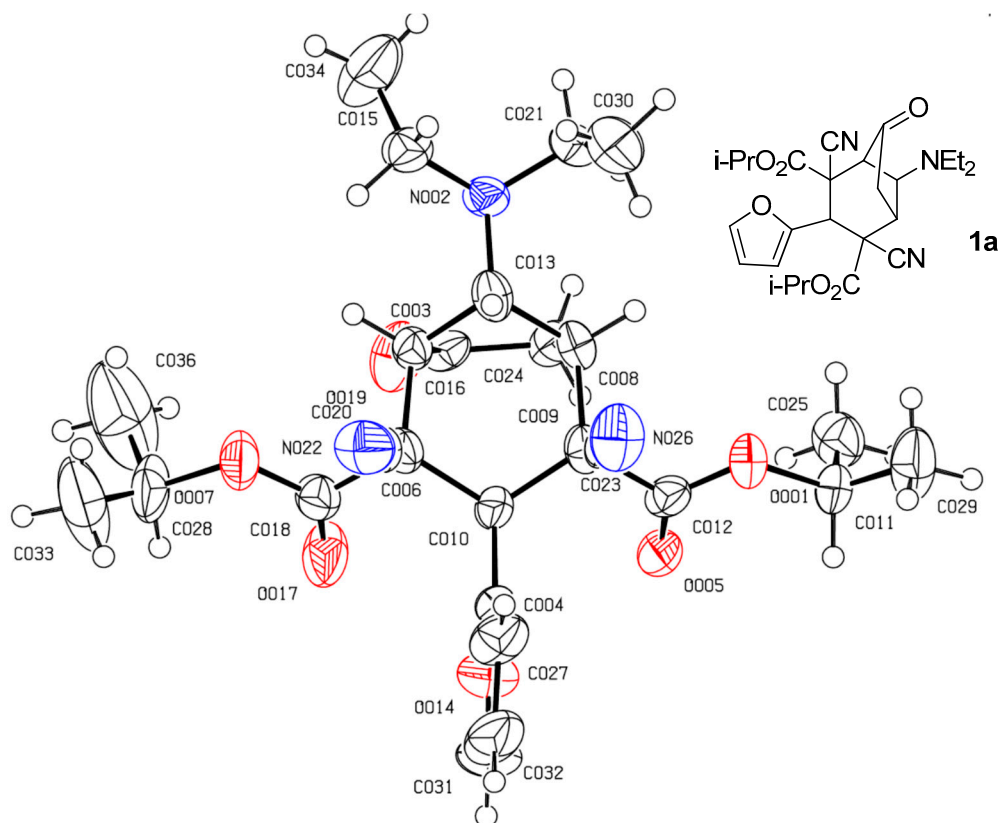
## Experimental

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  $^1\text{H}$ , 75 MHz for  $^{13}\text{C}$ ) in  $\text{CDCl}_3$ . The selected experimental procedure (synthesis of **1a**) is given. Microanalysis was obtained using a Carlo Erba 1106 analyzer.

A mixture of 0.83 mL (0.01 mol) of furfural and 0.02 mol of  $\text{Et}_2\text{NH}$  in 96% EtOH (10 mL) was stirred for 2 h. 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 h, and the precipitated crystals were filtered off.

Beige crystals, yield 37%, mp 154 °C (EtOH). IR,  $\nu$ ,  $\text{cm}^{-1}$ : 2240 ( $\text{C}\equiv\text{N}$ ), 1750 ( $\text{C}=\text{O}$ ), 1654 ( $\text{CO}_2\text{Pr-i}$ ). NMR  $^1\text{H}$  (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.02 t (6H, 2  $\text{CH}_2\text{CH}_3$ ,  $^3J$  7.0 Hz), 1.21–1.30 m (12H, 2  $\text{CH}(\text{CH}_3)_2$ ),

2.53–2.54 m (2H, H-7), 2.69 q (4H, 2  $\text{CH}_2\text{CH}_3$ ,  $^3J$  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  $\text{CH}(\text{CH}_3)_2$ ), 6.34 dd (1H, H-4<sub>furyl</sub>,  $^3J_{\text{H}(4)-\text{H}(3)}$  3.1 Hz,  $^3J_{\text{H}(4)-\text{H}(5)}$  1.7 Hz), 6.67 d (1H, H-3<sub>furyl</sub>,  $^3J_{\text{H}(4)-\text{H}(3)}$  3.1 Hz), 7.35–7.36 m (1H, H-5<sub>furyl</sub>). NMR  $^{13}\text{C}$  (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ , ppm: 11.1 (2  $\text{CH}_2\text{CH}_3$ ), 21.14 ( $\text{CH}(\text{CH}_3)_2$ ), 21.18 ( $\text{CH}(\text{CH}_3)_2$ ), 21.23 ( $\text{CH}(\text{CH}_3)_2$ ), 21.27 ( $\text{CH}(\text{CH}_3)_2$ ), 35.6 (C-3), 38.0 (C-1), 42.1 (2  $\text{CH}_2\text{CH}_3$ ), 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 ( $\text{CH}(\text{CH}_3)_2$ ), 72.9 ( $\text{CH}(\text{CH}_3)_2$ ), 110.79 (C-4<sub>furyl</sub>), 110.81 (C-3<sub>furyl</sub>), 115.3 (C $\equiv$ N), 116.2 (C $\equiv$ N), 142.8 (C-5<sub>furyl</sub>), 146.6 (C-1<sub>furyl</sub>), 163.4 ( $\text{CO}_2\text{Pr-}i$ ), 165.1 ( $\text{CO}_2\text{Pr-}i$ ), 206.9 (C=O). Found, %: C 64.62; H 6.97; N 8.63.  $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_6$ . Calculated, %: C 64.58; H 6.88; N 8.69.



**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).

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