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Synthesis of new functionalized 3,7-diazabicyclo[3.3.1]nonanes by aminomethylation of the Guareschi imides

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ABSTRACT

The aminomethylation of 4,4-dialkyl-2,6-dioxopiperidine-3,5-dicarbonitriles (Guareschi imides) was studied for the first time. When the Guareschi imides were treated with primary aliphatic amines and an excess of formaldehyde, 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles were obtained in varying yields (15–67%). The structure of 9,9-dimethyl-7-(2-methylpropyl)-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile was studied by X-ray diffraction analysis.

Introduction

3,7-Diazabicyclo[3.3.1]nonanes[1] (DABCNs, bispidines) are known as analgesics,[2] antitumor[3] and antiarrythmic[4] agents and also are of considerable interest as rigid pre-organized chelating bidentate ligands towards transition and main group metals.[5] One of the most convenient and effective protocols commonly used for the preparation of DABCNs is based on the double Mannich-type reaction of primary amines with aldehydes and *N*-substituted piperidin-4-ones or another suitable 3,5-binucleophilic partially saturated pyridine species.[1] In recent years our group has made significant progress in studying the reactivity of partially saturated pyridine species under Mannich conditions. It was shown that the aminomethylation of di- and tetrahydropyridine-2-chalcogenolates with aldehydes and primary amines strongly depends on the nature of a pyridine substrate and conditions, and the results are generally hardly predictable. Thus, a large variety of polyheterocyclic systems such as 3,7-diazabicyclo-[3.3.1]nonanes **1**,[6–10] pyrido[2,1-b][1,3,5]thiadiazines **2**,[11–19] pyrido[1,2-a][1,3,5]triazines **3**,[20–24] 3,5,7,11-tetraazatricyclo-[7.3.1.0^{2,7}]tridec-2-enes **4**,[25–34] dipyridotetrazocines **5**,[24] thiazolo[3,2-*a*]pyridines **6**,[35,36] pyrimido[4,3-b][1,3,5]thiadiazines **7**[37] and 3,7-diazabicyclo[3.3.1]non-3-enes **8**[38] were obtained in this way (Scheme 1). 3,5-Dicyano-2,6-piperidinediones **9**, also known as Guareschi imides, were first prepared by pseudo four component reaction of ketones and ammonia with two molecules of ethyl cyanoacetate,[39] and widely used as precursors in the synthesis of β,β-disubstituted glutarates and other compounds of pharmacological interest.[40] It is worth mentioning that 3,5-dicyano-2,6-piperidinediones also are known to exhibit analgesic properties.[41] Due to the presence of two C-nucleophilic centers (C-3 and C-5) and imide C(O)NHC(O) fragment in the molecule, Guareschi imides are of interest as they are expected to react under Mannich conditions to give either DABCNs, 3,7-diazabicyclo[3.3.1]non-3-enes or monocyclic aminomethylation products. To our surprise, a survey of literature revealed that, while the aminomethylation of 6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-olates **10** (which could be considered formally as Guareschi imides salts) as well as their sulfur- and selenium analogs (Scheme 2) is well documented,[6–10,38] the literature lacked a report on the Mannich reaction with long-known Guareschi imides **9**.

In continuation to our studies, herein we wish to report, for the first time to our knowledge, a one-pot Mannich-type synthesis of novel 3,7-diazabicyclo[3.3.1]nonanes **11** starting from the classical Guareschi imides **9**.

Results and discussion

Glutarimides **9a,b** were prepared by the known methods.[39a,42] We found that upon treatment of **9a,b** with primary aliphatic

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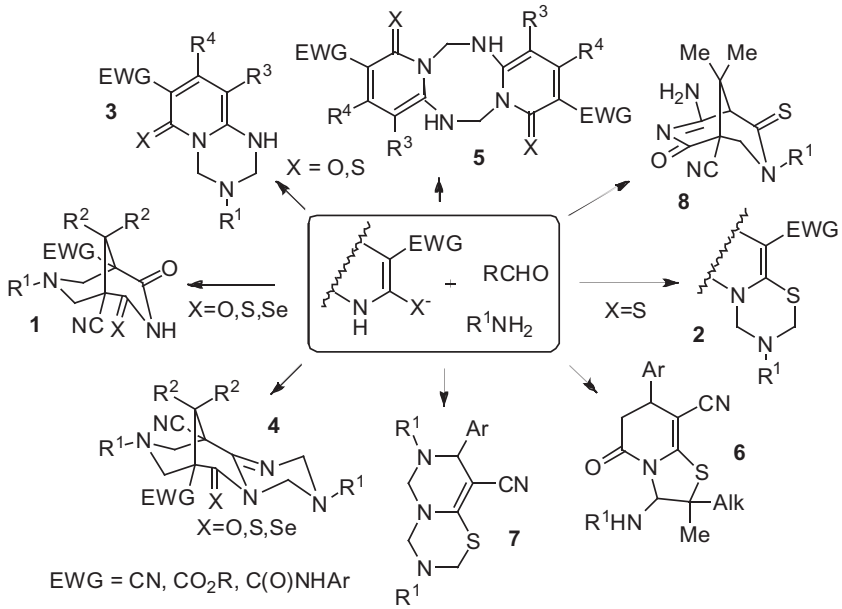
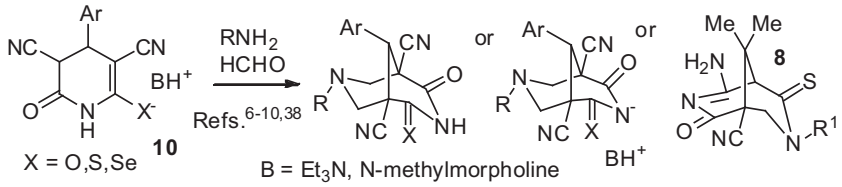


Scheme 1. A diversity of Mannich-type products derived from partially saturated pyridine-2-chalcogenolates.



Scheme 2. The aminomethylation of 1,4,5,6-tetrahydropyridine-2-chalcogenolates **10**.

Table 1
Structures and yields of diazabicyclononanes **11a–i**.

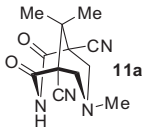
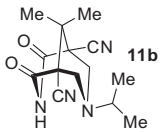
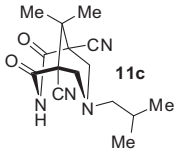
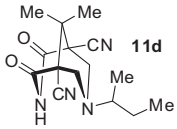
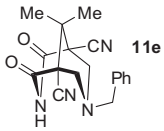
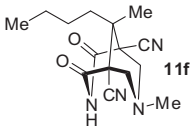
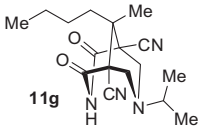
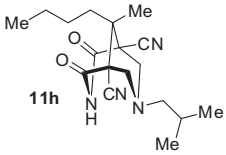
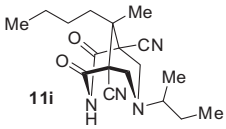
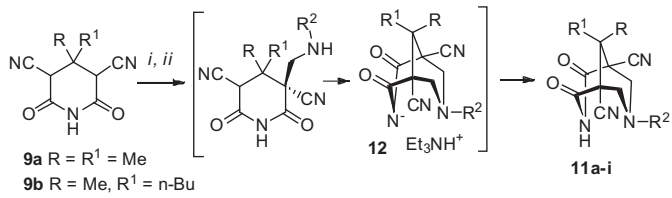
Starting compound	R^2NH_2	Product	Yield (%)
9a	$MeNH_2$	 **11a**	39
9a	*i*-$PrNH_2$	 **11b**	54
9a	*i*-$BuNH_2$	 **11c**	41
9a	*sec*-$BuNH_2$	 **11d**	58
9a	$PhCH_2NH_2$	 **11e**	19

Table 1 (*continued*)

Starting compound	R^2NH_2	Product	Yield (%)
9b	$MeNH_2$	 **11f**	67
9b	*i*-$PrNH_2$	 **11g**	24
9b	*i*-$BuNH_2$	 **11h**	27
9b	*sec*-$BuNH_2$	 **11i**	15

amines (2 eq) and an excess of 37% aq. HCHO, the desired 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles **11a–i** were formed (Scheme 3), albeit in low yields (generally up to 30%). The yields of DABCNs **11** were significantly improved by



Scheme 3. Synthesis of DABCNs **11a–i**. Reagents and conditions: *i*: R^2NH_2, 37% aq. HCHO, Et_3N (cat.), EtOH, Δ, 2 min; *ii*: aq. HCl to pH 6.

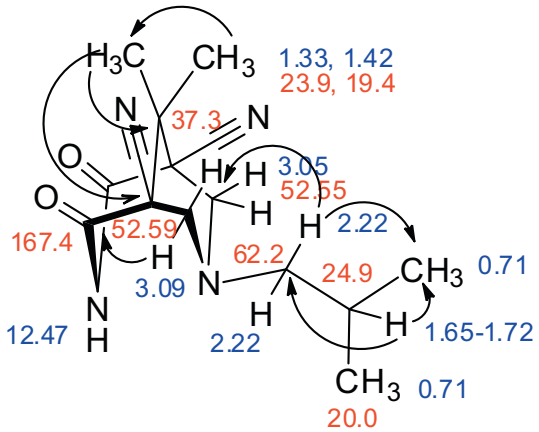


Fig. 1. The principal correlations in the ^1H–^{13}C HMBC NMR spectrum of compound **11c**.

addition of a tertiary amine as a catalyst. Thus, the yield of DABCN **11f** was improved from 26% to 67% after addition of few drops of Et_3N. The yields and structures of the DABCNs **11a–i** are given in Table 1.[43] The pH value of the reaction mixture should be adjusted precisely to pH 6.0 with a few drops of diluted aq. HCl at the final step, to avoid contamination of the product with bispidine salts **12** formed during the reaction.

DABCNs **11a–i** were obtained as white, finely crystalline solids, insoluble in water or ether, sparingly soluble in hot EtOH and moderately soluble in Me_2CO or DMSO. The structure and purity of the obtained compounds **11a–i** were confirmed by ^1H and ^{13}C NMR data including DEPTQ and APT experiments, IR spectroscopy, LC/MS and elemental analysis data. The infrared spectra exhibited absorption bands due to the unconjugated cyano groups at ν 2250–2262 cm^{-1}, N—H and amide C=O bonds at ν 3098–3470 cm^{-1} and 1700–1750 cm^{-1}, respectively. The ^1H NMR spectra of bispidines **11a-i** revealed the signals of two methylenes 6-CH_2 и 8-CH_2 as two pairs of doublets at δ 2.96–3.07 ppm и δ 3.08–3.37 ppm (^2J = 11.5–12.1 Hz). The signals of NH protons were observed at δ 12.34–12.57 ppm. A complete assignment of ^1H and ^{13}C NMR signals for bispdines **11** was based on the analysis of 2D NMR ^1H–^{13}C HSQC and ^1H–^{13}C HMBC spectra for 7-isobutyl-9,9-dimethyl-2,4-dioxo-3,7-diazabicyclo[3.3.1]-nonane-1,5-dicarbonitrile **11c** (for details see Supplementary materials). The most significant correlations of ^1H–^{13}C HMBC NMR spectrum for compound **11c** are shown in Fig. 1.

In addition, the structure of 7-isobutyl-9,9-dimethyl-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile **11c** was confirmed by X-ray structural analysis (Fig. 2).[44]

Another point we have to discuss is the stereo configuration at C-9 position in the compounds **11f-i**. According to NMR data, these compounds exist as the sole stereoisomers. To date, we have no clear indication or any NMR evidences whether C(9)-butyl and N(7)-alkyl have *trans*- or *cis*-orientation. However, there are some considerations indirectly pointing to the suggested *trans*-orientation. First, the aminomethylation of Guareschi imides should rather occur from the less hindered side. Second, the X-ray data[29] for the related compound bearing DABCN moiety showed *trans*-orientation of the Mannich-derived bulky CH_2NArCH_2 fragment and an aryl substituent at C-9 position.

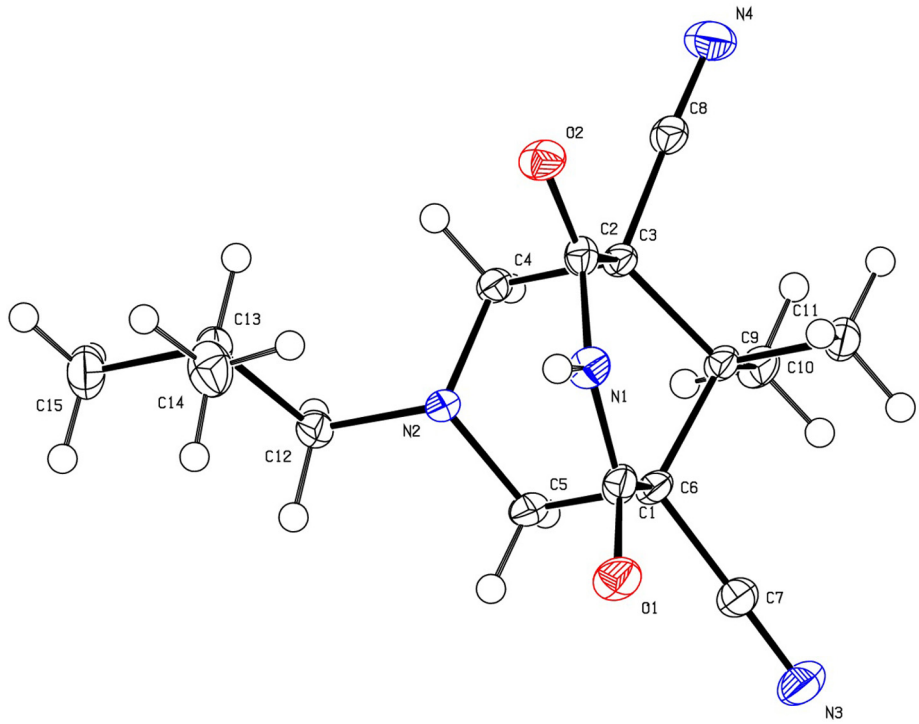


Fig. 2. The molecular structure of compound **11c** with atoms represented by thermal vibration ellipsoids of 50% probability.

Conclusion

In summary, we report the first synthesis of new functionalized 3,7-diazabicyclo[3.3.1]nonanes, starting from the long-known and easily available 2,6-dioxopiperidine-3,5-dicarbonitriles (Guareschi imides). Being close analogs of 4-aryl-2,6-dioxopiperidine-3,5-dicarbonitriles, the classical 4,4-dialkyl substituted Guareschi imides showed the same behavior in Mannich reaction resulted in the formation of 3,7-diazabicyclo[3.3.1]nonanes. The operationally simple one-pot approach is based on the base-catalyzed Mannich reaction of Guareschi imides with HCHO and primary amines. This approach would broaden the chemistry of Guareschi imides and related pyridine species and hold great potential in the synthesis of bispidine-type compounds.

Acknowledgments

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Conflicts of Interests

Authors declare no conflicts of interests.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.069.

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43. *Typical procedure for the preparation of 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles* **11a–i**. To a suspension of Guareschi imide **9a,b** (1.0 mmol) in 96% EtOH (20 mL), triethylamine (2-3 drops), a primary amine (2.2 mmol) and 37% aq. HCHO (2.0 mL, 26.6 mmol) were added in succession. The mixture was stirred for 1 min, then refluxed under vigorous stirring for 2 min, and the hot solution was rapidly filtered through a paper filter. After 12 h, the pH value was adjusted to pH 6.0 with diluted aq. HCl. The precipitate formed was left for 6 h at ambient temperature, filtered off, washed with EtOH to give pure DABCNs **11a–i**. The compounds could be recrystallized from acetone-EtOH mixture (1:1).
44. Crystallographic data (including structure factors) for the structure **11c** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 1562481**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.