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Stereocontrolled intramolecular cyclization of *anti*-β-aminonitriles. Convenient access to *trans*-azetidin-2-imines

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Dedicated to Academician Ivan Juchnovski on the occasion of his 70th birthday

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We have developed a convenient approach to synthesis of *trans*-azetidin-2-imines, consisting in stereocontrolled cyclization of *anti*-*β*-amino nitriles in boiling ethanol in the presence of hydrochloric acid.

Key words: azetidin-2-imine, intramolecular cyclization, *β*-amino nitrile

INTRODUCTION

In spite of the amount of research addressed to synthesis of β-lactams, one of the most successful groups of antibiotics, very few studies have been devoted to the preparation of the corresponding imine derivatives.

The first examples of the azetidine 2-imine small-ring heterocyclic system have been reported in the early 1975 [1]. The products have been obtained in reaction of N-isopropylallenimine with organic azides. Later on, Gaudemare *et al*. demonstrated that the addition of organozinc reagents of α-bromonitriles to aldimines in THF resulted in formation of substituted azetidine 2-imines in good yields [2].

Ghosez *et al*. [3] developed a general approach to synthesis of azetidin-2-iminium salts, which have been used as valuable precursors in synthesis of various four-membered heterocycles like 2-amino-azetines [4, 5], β-lactams and their sulphur analogues azetidine-2-thiones [6–8] and azetidine-2-imines [8].

Data concerning the stereochemical course in the cyclization reaction are scarce [7, 9] and to the best of our knowledge only one paper deals with the preferential formation of *cis* or *trans* product as a function of the steric and electronic demands of the reactants [7].

Recently, in our study on the diastereoselectivity in addition of lithiated nitriles to Schiff bases we observed fast proton shift in the initially formed azanion, resulting in a prochiral carbanionic intermediate with an adjacent chiral centre [10]. The subsequent one-pot alkylation reaction was found to proceed with high to outstanding level of anti diastereoselectivity, thus giving convenient access to relatively complex molecules with definite configuration.

In an attempt for acidic hydrolysis of a casually selected example of the alkylated compounds, more precisely *anti*-2-methyl-2,3-diphenyl-3-phenylamino-propionitrile instead of the corresponding β-amino-acid, we isolated a product which was specified as 3-methyl-1,3,4-triphenylazetidine-2-imine.

Taking into account this finding and with readily available *anti*-β-aminonitriles in hands, it was of interest to explore the applicability of the above-mentioned approach to the synthesis of new representatives of this small, scarcely presented in the chemical structural space heterocycle. An additional reason to perform this study was our anticipation that starting from stereochemically pure β-amino-nitriles with *anti*-configuration, we would obtain stereochemically pure azetidine-2-imines as a result of a stereocontrolled cyclization.

Herein we present our study on the cyclization of some β-aminonitriles to differently functionalized azetidine-2-imines under acidic conditions.

RESULTS AND DISCUSSION

The synthesis (Scheme 1) was performed in boiling methanol in the presence of conc. hydrochloric acid for 4 hours. The target compounds were isolated after a common work-up procedure, followed by purification with flash chromatography on silica gel (see Experimental section). In all cases studied, only one of the two possible isomers was isolated. The structure of all new products was unambiguously proved using a set of spectral techniques and elemental analysis.

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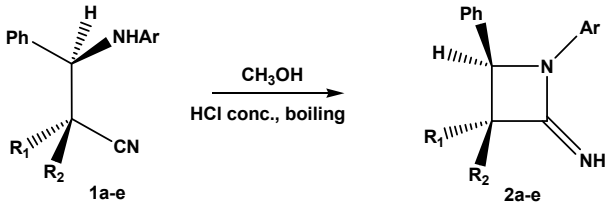
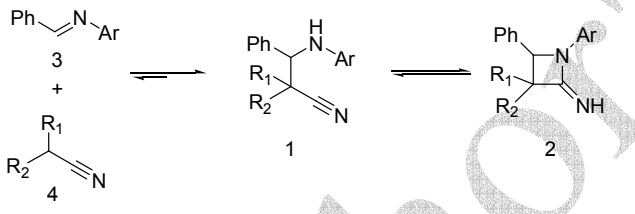


	Ar	R_1	R_2
a	Ph	Ph	CH_3
b	β-naphthyl	Ph	CH_3
c	Ph	Ph	$CH_2CH{=}CH_2$
d	β-naphthyl	Ph	$CH_2CH{=}CH_2$
e	Ph		CH_3

Scheme 1: Synthesis of azetidine-2-imines **2**a–**2**e.

The reaction occurs with good to moderate yields. The optimal reaction time was determined by monitoring the reaction using ^{1}H NMR and TLC analysis. It was clearly demonstrated that the prolongation of the reaction duration above 4 hours resulted not in an increase of the reaction yields, but in decomposition of the starting β-aminonitriles as shown in Scheme 2.



Scheme 2: Cyclization and decomposition of β-aminonitriles.

To realize the stereochemical course of the reaction, we took in mind the following consideration. Since the cyclization does not concern the existing stereogenic centres, the configuration of the cyclic azetidine-2-imines must be in immediate relation with the configuration of the β-aminonitrile precursors. Hence, starting from configurationally pure *anti*-isomers **1a**–**1e** we should obtain *trans*-azetidin-2-imines **2a**–**2e**. This presumption was undoubtedly confirmed by ^{1}H NMR analysis of the crude reaction mixtures where no signals for the second possible *cis*-stereoisomer were detected. An attempt for visualization of the relationship between the stereochemistry of the starting adducts and the resulting azetidine-2-imines is presented in Scheme 1.

Thus, the assigned *trans*-configuration was confirmed in an independent way by the NOESY experiments, carried out in the case of **2e**. The experiments proved unambiguously the *trans*-location of the phenyl group and the R_2 substituent at the adjacent stereogenic centres. Some characteristic NOESY correlations are presented in Fig. 1.

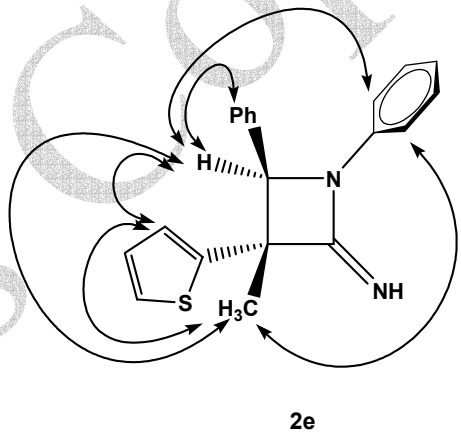
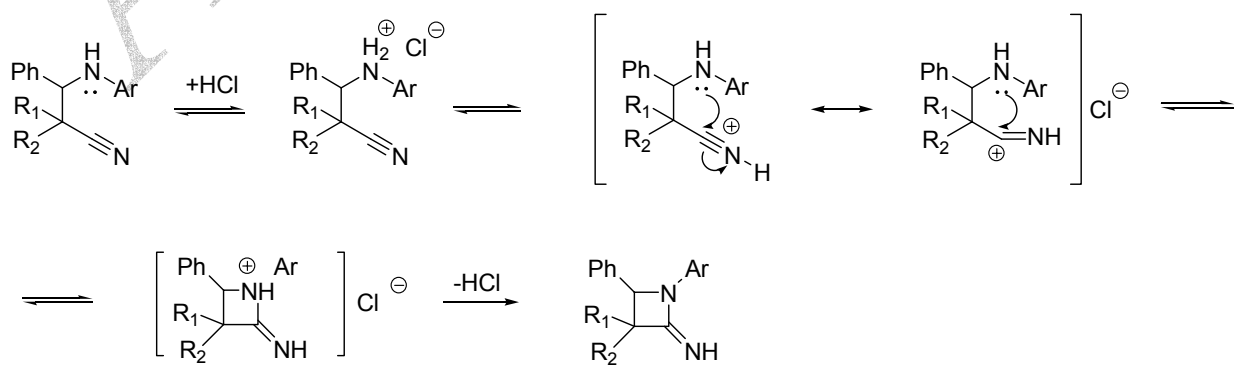


Fig. 1. Arrows indicate the important NOE effects in compound 2e.

As reported, cyclization occurs in the presence of hydrochloric acid, e.g. under acidic conditions. Our attempts to perform the synthesis in neutral medium were unsuccessful. As could be expected, protonation of the nitrile group increases its electrophilicity and makes possible closing of the azethidin-2-imine heterocycle. The probable mechanism of cylization is depicted in Sheme 3:



Scheme 3. Probable reaction mechanism of the cyclization reaction.

In conclusion, the present paper reports a new and convenient approach to synthesis of differently functionalized *trans*-azetidie-2-imines, consisting in stereocontrolled cyclization of *anti*-β-aminonitiles in acidic medium. The paper contributes to the synthetic diversity of scarcely presented azetidine-2-imine small heterocyclic system.

EXPERIMENTAL

The solvents were commercially available and used without further purification. The starting *anti*-β-aminonitiles **1a**–**1e** were synthesized as described [10]. Compound **1e** is newly prepared for the purposes of the present investigation and described in Experimental. Flash chromatography was carried out using Fluka silica gel 60 (0.04–0.063 mm). Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 plates. Melting points were determined on a Kofler apparatus and were not corrected. IR spectra were recorded on a Bruker FTR-113 V spectrometer using KBr pellets and only partial data are reported. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-250 spectrometer using TMS as an internal standard. The chemical shifts are reported in ppm on the δ scale relative to TMS (tetramethylsilane, δ = 0 ppm); J = Hz; C-multiplicities were assigned by DEPT techniques. EI-MS (30 eV) were recorded on a Hewlett Packard 5973 device. Elemental analysis was performed by the Micro-analytical service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

Anti-2-methyl-3-phenyl-3-(phenylamino)-2-(thiophen-2-yl)propanenitrile (**1e**): The starting compound **1e** was obtained for the purposes of the present study as described [10]. Thus, from 2-thiophenyl-acetonitrile (123 mg, 1 mmol), benzylideneaniline (181 mg, 1 mmol) and methyl iodide (213 mg, 1.5 mmol) the title compound *anti*-**1e** was isolated by recrystallization (EtOH) (150 mg, 47%). M.p. 104–106ºC. R_f = 0.3 (Et_2O/hexane = 1:3). $C_{20}H_{18}N_2S$ (318.44): calcd. C 75.44; H 5.70; N 8.80; S 10.07; found: C 75.30, H 5.43, N 8.43, S 9.84. MS (EI, 30eV): m/z = 318 $[M]^+$. ^{1}H NMR ($CDCl_3$):1.69 (s, 3H, CH_3), 4.29 (d, J = 6.5, 1H, NH), 4.53 (d, J = 6.5, 1H, CH), 6.42–6.46 (m, 2H, $CH_{thienyl}$), 6.62–6.68 (m, 1H, $CH_{thienyl}$), 6.96–7.06 (m, 3H, CH_{phenyl}), 7.25–7.30 (m, 1H, CH_{phenyl}), 7.30–7.42 (m, 6H, CH_{phenyl}). ^{13}C NMR ($CDCl_3$): 26.9 (CH_3), 45.8 (C_q), 66.7 (CH), 114.2, 118.6 (CH), 120.8 (CN), 126.0, 126.8, 126.83, 128.11, 128.58, 128.65, 129.0, 137.7 (C_q), 142.1 (C_q), 146.25 (C_q).

General experimental procedure for synthesis of 1,3,4 substituted azetidin-2-imines ***2a-e***

The starting β-aminonitrile (1 mmol) was dissolved in methanol (20 ml). Conc. hydrochloric acid (3 ml) was then added and the reaction mixture was kept under reflux for 4 hours. After cooling, the solvent was removed under reduced pressure to half of the volume, diluted with cold water and neutralized to pH = 7 with solid Na_2CO_3. The solution was extracted with CH_2Cl_2, the combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The target compounds were purified by column chromatography on silica gel. Thus isolated products are spectroscopically and analitycally pure. Additional recrystallisation from EtOH decreases significantly the reaction yields without appreciable effect on the product purity.

Trans-3-methyl-1,3,4-triphenylazetidin-2-imine (**2a**): Following the general experimental procedure, starting from 1a (312 mg, 1 mmol) the title compound *trans*-**2a** (187 mg, 60%) was isolated after purification by column chromatography (silica gel, Et_2O/hexane = 1:1). Recrystallization (EtOH) afforded **2a** (140 mg, 40%) as white crystals, m.p. 134–136ºC. R_f = 0.29 (Et_2O/hexane = 1:1). $C_{22}H_{20}N_2$ (312.41): calcd. C 84.58, H 6.45, N 8.97, found C 84.39, H 6.33, N 8.78. MS: m/z = 312 $[M]^+$. IR: ν = 1675 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.23 (s, 3 H, CH_3), 5.13 (s, 1H, CH), 6.95–7.44 (m, 15H, 3×Ph). ^{13}C NMR ($CDCl_3$): 18.8 (CH_3); 57.7 (C_q); 70.6 (CH–Ph); 116.7, 122.1, 125.8, 126.8, 127.3, 128.0, 128.6 and 128.9 (CH_{arom}); 135.4, 139.6 and 142.3 (C_q), 169.1 (C=NH).

Trans-3-methyl-1-(naphthalen-2-yl)-3,4-diphenyl-azetidin-2-imine (**2**b): Following the general experimental procedure, starting from **1b** (362 mg, 1 mmol) the title compound *trans*-**2b** (238 mg, 66%) was isolated after purification by column chromatography (silica gel, Et_2O/hexane = 1:1). Recrystallization (EtOH) afforded **2b** (144 mg, 40%) as white crystals. M.p. 185–187ºC, R_f = 0.32 (Et_2O/hexane = 1:1). $C_{26}H_{22}N_2$ (362.47):calcd. C 86.15, H 6.12, N 7.73, found C 86.02, H 5.93, N 7.51. MS: m/z = 362 $[M]^+$. IR: ν = 1679 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.19 (s, 3H, CH_3), 5.19 (s, 1H, CH), 7.18–7.70 (m, 17H, H_{arom}). ^{13}C NMR ($CDCl_3$): 18.8 (CH_3); 57.8 (C_q); 70.9 (CH–Ph); 112.9, 117.5, 124.2, 125.8, 126.4, 126.9, 127.2, 127.4, 127.6, 128.1, 128.7, 128.8, 129.0 and 129.5 (CH_{arom}); 133.8, 135.4, 137.2 and 142.2 (C_q); 169.3 (C=NH).

3-Allyl-1,3,4-triphenylazetidin-2-imine (**2c**): Following the general experimental procedure, starting from **1c** (338 mg, 1 mmol) the general experimental procedure afforded the title compound *trans*-**2c** (100 mg, 30%) after purification by column chromatography (silica gel, Et_2O/hexane = 1:1). Recrystallization (EtOH) gave access to **2c** (50 mg, 15%) as white crystals. M.p. 152–154ºC. R_f = 0.35 (Et_2O/hexane = 1:1). $C_{24}H_{22}N_2$ (338.44): calcd. C 85.17, H 6.55, N 8.28, found C 84.94, H 6.42, N 8.00. MS: m/z = 338 $[M]^+$. IR: ν = 1669 cm^{-1}. ^1H NMR ($CDCl_3$): 1.56 (br., NH), 2.22–2.40 (m, 2H, CH_2), 4.92–5.01 (m, 2H, CH_2=), 5.12 (s, 1H, CH–Ph), 5.40–5.55 (m, 1H, CH=), 6.93–7.56 (m, 15H, 3×Ph). ^{13}C NMR ($CDCl_3$): 38.25 (CH_2); 60.42 (C_q); 70.58 (CH–Ph); 116.74 (CH); 118.95 (CH_2=); 122.05, 126.49, 127.08, 127.36, 128.25, 128.76, 128.83, 129.04 and 132.94 (CH_{arom}), 135.28, 139.68 and 140.48 (C_q); 167.11 (C=NH).

3-Allyl-1-(naphthalen-2-yl)-3,4-diphenylazetidin-2-imine (**2d**): Following the general experimental procedure, starting from **1d** (388 mg, 1 mmol) the title compound *trans*-**2d** (116 mg, 30%) was isolated after purification by column chromatography (silica gel, Et_2O/hexane = 1:1). Recrystallization (EtOH) afforded **2d** (70 mg, 18%) as white crystals. M.p. 166–168ºC. R_f = 0.48 (Et_2O/hexane = 1:1). $C_{28}H_{24}N_2$ (388.5): calcd. C 86.56, H 6.23, N 7.21; found C 86.33, H 6.00, N 6.99. MS: m/z = 388 $[M]^+$. IR: ν = 1669 cm^{-1}. ^1H NMR ($CDCl_3$): 2.27–2.44 (m, 2H, CH_2), 4.95–5.05 (m, 2H, CH_2=), 5.26 (s, 1H, CH), 5.46–5.52 (m, 1H, CH=), 7.35–7.73 (m, 17H, CH_{arom}). ^{13}C ($CDCl_3$+$DMSO_{d6}$): 36.3 (CH=); 57.7 (CH_2); 71.5 (CH–Ph); 117.8 and 118.5 (CH), 118.8 (CH_2=); 126.0, 126.4, 126.5, 127.0, 127.2, 127.4, 128.1, 128.2, 128.5, 128.8 and 128.9 (CH_{arom}); 130.5, 130.7, 131.1, 132.1 and 135.9 (C_q); 165.8 (C=NH).

3-Methyl-1,4-diphenyl-3-(thiophen-2-yl)azetidin-2-imine (**2e**): Following the general experimental procedure, starting from **1e** (318 mg, 1 mmol) the title compound *trans*-**2e** (130 mg, 41%) was isolated after purification by column chromatography (silica gel, Et_2O/hexane = 1:1). Recrystallization (EtOH) afforded **2e** (60 mg, 19%) as white crystals. M.p. 134–136ºC. R_f = 0.27 (Et_2O/hexane = 1:1). $C_{20}H_{18}N_2S$ (318.44): calcd. C 75.44, H 5.70, N 8.80, S 10.07, found 75.39, H 5.49, N 8.63, S 9.90. MS: m/z = 318 $[M]^+$. IR: ν = 1673 cm^{-1}. ^1H NMR ($CDCl_3$): 1.26 (s, 3H, CH_3), 5.24 (s, 1H, CH), 6.99–7.08 (m, 3H, $CH_{thiophene}$), 7.24–7.30 (m, 5H, CH_{arom}), 7.33–7.40 (m, 5H, CH_{arom}). ^{13}C ($CDCl_3$): 20.3 (CH_3); 55.3 (2-C) C_q; 71.2, 116.9, 122.3, 123.9, 124.7, 126.8, 127.2, 128.2, 128.7 and 128.9, (CH), 135.0, 139.7 and 146.1 (C_q); 168.3 (C=NH).

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СТЕРЕОКОНТРОЛИРАНА ВЪТРЕШНОМОЛЕКУЛНА ЦИКЛИЗАЦИЯ НА *анти*-β-АМИНО-НИТРИЛИ. УДОБНА СИНТЕЗА НА *транс*-АЗЕТИДИН-2-ИМИНИ

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Посветена на акад. Иван Юхновски по повод на 70-та му годишнина

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(Резюме)

Разработен е удобен метод за получаване на *транс*-азетидин-2-имини, включващ стереоконтролирана циклизация на *анти*-β-амино нитрили в кипящ етанол в присъствие на солна киселина.