A Novel Ring Enlargement of 2H-Azirine-3-methyl(phenyl)amines via Amidinium-Intermediates: A New Synthetic Approach to 2,3-Dihydro-1,3,3-trimethylindol-2-one

Mekhael, Maged K G; Smith, Richard J; Bienz, Stefan; Linden, Anthony; Heimgartner, Heinz

Abstract: 2,2,N-T trimethyl-N-phenyl-2H-azirin-3-amine (1a) was prepared by successive treatment of 2,N-dimethyl-N-phenylpropanamide (18) with phosgene, triethylamine, and sodium azide. Reaction of 1a in THF solution with boron trifluoride gave 2-amino-1,3,3-trimethyl-3H-indolium tetrafluoroborate (19) in high yield. The latter reacted with acetic anhydride in pyridine to give a mixture of N-(2,3-dihydro-1,3,3-trimethylindol-2-yliden)acetamide (22) and 2,3-dihydro-1,3,3-trimethylindol-2-one (21). On hydrolysis with aqueous HCl, 22 was converted to 21. The molecular structures of 19 and 22 were established by X-ray crystal structure determination.

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A Novel Ring Enlargement of 2H-Azirine-3-methyl(phenyl)amines via Amidinium-Intermediates: A New Synthetic Approach to 2,3-Dihydro-1,3,3-trimethylindol-2-one [1]*

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2H-Azirine-3-amines, Ring Enlargement, 2,3-Dihydroindol-2-ones
2,2,N,N-Trimethyl-N-phenyl-2H-azirin-3-amine (1a) was prepared by successive treatment of 2,N-dimethyl-N-phenylpropanamide (18) with phosgene, triethylamine, and sodium azide. Reaction of 1a in THF solution with boron trifluoride gave 2-amino-1,3,3-trimethyl-3H-indoliun tetrafluoroborate (19) in high yield. The latter reacted with acetic anhydride in pyridine to give a mixture of N-(2,3-dihydro-1,3,3-trimethylindol-2-yliden)acetamide (22) and 2,3-dihydro-1,3,3-trimethylindol-2-one (21). On hydrolysis with aqueous HCl, 22 was converted to 21. The molecular structures of 19 and 22 were established by X-ray crystal structure determination.

Introduction

Since the first synthesis of a 2H-azirin-3-amine by Rens and Ghosez [2], these compounds have proven to be versatile building blocks for the preparation of heterocycles as well as of peptides containing \( \alpha, \alpha \)-disubstituted glycines [3]. It has been shown that, depending on the reaction conditions, each of the three ring bonds can be cleaved selectively leading to reactive intermediates such as nitrile ylides and 2-azabuta-1,3-dienes (C-C cleavage) and 1-azaallyl cations (C-N cleavage) [2, 4, 5]. On the other hand, the competing addition of a nucleophile, e.g. a carboxylate, onto 2 yields an aziridine 5 which rearranges to a 2-(acylamino)carboxamide 6 (cf. [6–9] and refs. cited therein).

Of special interest are reactions of 1 with NH-acidic heterocycles (pK_a < 8) leading to new heterocycles with a ring enlarged by three atoms (N-C). This rather general ring enlargement reaction proceeds via an intermediate aziridine of type 8 followed by two consecutive ring expansions (8→9→10, Scheme 2) [10]. Examples for 7- to 12-membered products 10–12, obtained from 4- to 9-membered starting materials (e.g. 4,4-dialkylisoxazolidin-3-one [11] and 3-oxosultams of different ring size [3, 12–16]) are shown in Scheme 2.

The reaction of 1 with trifluoroacetamide gives 4H-imidazoles 15a [17]. A conceivable reaction mechanism via aziridine 13 and zwitterion 14 which parallels that of the ring enlargement 7→10 is shown in Scheme 3. A serious limitation of this reaction is the acidity of the amides as only substances with pK_a < 8 are able to activate 1 by protonation (pK_a of 1, R^1–R^4 = Me: 7.1 [18]). Therefore, neither benzamide nor acetamide react with 1. Recently, we were able to overcome this hurdle by activating 1 with boron trifluoride. This complex 16 was shown to react at low temperature...
with the sodium salt of carboxamides to give the corresponding 4H-imidazoles 15 (Scheme 3). We propose that aziridine 17 is an intermediate that undergoes a ring enlargement analogous to 13→14→15a.

The activation of 1 by treatment with boron trifluoride has also been used in the reactions with enolates of esters, thiosteres, and carboxamides to give 1,5-dihydro-2H-pyrrol-2-ones, and even the enolate of acetophenone reacts with the BF₃-complex of 1 leading to a 2H-pyrrol-3-amine derivative [19]. Furthermore, these complexes undergo reactions with α-amino acid esters in which 3,6-dihydropyrazin-2(1H)-ones are formed as the main product; the same products are obtained when 2H-azirin-3-amines 1 are reacted with α-amino acid ester hydrochlorides [20].

In the present paper, we present the first results of a novel ring enlargement reaction of 2,2,3,N-trimethyl-N-phenyl-2H-azirin-3-amine (1a, R¹−R³ = Me, R⁴ = Ph) with BF₃ in the absence of external nucleophiles leading to a 2,3-dihydroindol-2-one (indoline-2-one).
Results and Discussion

The starting material Iα [21] was prepared from 2,N-dimethyl-N-phenylpropanamide (18) according to the protocol of Rens and Ghosez [2] (see also [3, 22]). Addition of an equimolar amount of BF₃·OEt₂ to a stirred solution of Iα in THF or Et₂O at −78 °C gave 2-amino-1,3,3-trimethyl-3H-indolium tetrafluoroborate (19) in up to 81.5% yield as colorless crystals (m.p. 246.5–247.7 °C) (Scheme 4). The structure of the product has been established on the basis of its spectroscopic data, elemental analysis, and an X-ray crystal structure analysis (Fig. 1). The most characteristic data are three strong absorptions at 1695, 1680, and 1610 cm⁻¹ in the IR spectrum (KBr), two NH signals (δ = 10.07 and 9.77 ppm), a singlet for MeN at δ = 3.49 ppm (¹H NMR, D₆-DMSO), and a singlet at δ = 175.6 ppm (¹³C NMR, D₆-DMSO) for C(2) of the indolium ring. In the crystal structure, the extraannular N(2)–C(2) bond is slightly shorter (1.305(4) Å) than the intraannular N(1)–C(2) bond (1.333(4) Å, Table 1), which suggests delocalization of the formal double bond and the cationic charge across the N(1)–C(2)–N(2) region of the cation. The ring system of the indolium cation is planar including the Me group at N(1). Each H atom of the terminal amino group forms an interionic hydrogen bond with an F atom; the two interactions being with different anions. These interactions link two cations and two anions into a centrosymmetric C⁺⋯A⁻⋯C⁺⋯A⁻ loop with a secondary graph set motif [24] of R₄⁺ [12]. The unitary graph set motif for each individual interaction is D.

Treatment of an aqueous solution of 19 at 0 °C with aqueous NaOH (30%) and extraction with dichloromethane gave a yellow oily substance 20.
which, according to the spectroscopic data and elemental analysis, is either a hydrate of 2,3-dihydro-1,3,3-trimethylindol-2-imine or the corresponding indolium hydroxide. This product was transformed to the known [25] 2,3-dihydro-1,3,3-trimethylindol-2-one (21, Scheme 4) in modest yield upon refluxing in H₂O/THF.

Reaction of the tetrafluoroborate 19 with acetic anhydride in pyridine at ca. 23 °C for 16 h, followed by aqueous workup and chromatographic separation led to N-(2,3-dihydro-1,3,3-trimethylindol-2-yliden)acetamide (22) and 21 as colorless crystals (m.p. 61.8–62.1 and 49.7 °C, respectively) in a ratio of ca. 2:1 (Scheme 5). Most likely, the N-acetyl derivative 22 has partly been hydrolysed under the workup conditions. Compound 22 could also be obtained from 20 when the latter was treated with acetic anhydride in pyridine. Hydrolysis of 22 with aqueous HCl gave the indolin-2-one 21.

The structure of 22 was determined on the basis of the spectroscopic data and elemental analysis. The IR spectrum (KBr) shows strong absorptions at 1711, 1651, and 1606 cm⁻¹. Three signals for Me groups appear in the ¹H and ¹³C NMR spectra (CDCl₃): at δ = 3.20/27.3 ppm for MeN, at 2.29/28.3 for MeCO, and at 1.51/25.9 for Me₂C(3). It is worth mentioning that the two Me groups at C(3) show only one signal, i.e. the N-acetyl group freely rotates under the NMR conditions. In the EI-MS, the most characteristic peaks are at m/z 216 (M⁺), 201, 186, 175, and 160. Finally, the structure was proved by an X-ray crystal structure determination (Fig. 2). The fused rings form an almost planar system. Atom N(2) of the exocyclic C=N bond deviates significantly by 0.21 Å from this plane and the C=O bond is not coplanar with the C=N bond [torsion angle O(11)–C(11)–N(2)–C(2) 62.5(3)°], which indicates reduced conjugation in this region of the molecule. For a comparison, the C,N-bond lengths of 19 and 22 are listed in Table 1.

**Reaction mechanisms**

Although we have previously studied BF₃-catalyzed reactions of 2H-azirine-3-amines 1 in the presence of nucleophilic reagents, the ring enlargement to indole derivatives described in the present paper has never been observed before. Obviously, the external nucleophiles react efficiently by addition onto the amidinium C atom to give an aziridine (cf. 17, Scheme 3). The ring opening to a 1-azaallyl cation has only been observed for protonation in the absence of a nucleophile (Scheme 1). In the presently described ring enlargement of 1a to the indole derivative 3, the N-
Table 1. CN bond lengths (Å) in the crystal structures of 19 and 22.

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<th>Atom</th>
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<th>22</th>
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<td>1.370(2)</td>
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<td>1.455(2)</td>
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<tr>
<td>N(2)–C(2)</td>
<td>1.305(4)</td>
<td>1.282(2)</td>
</tr>
<tr>
<td>N(2)–C(11)</td>
<td>1.386(2)</td>
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</tr>
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</table>

phenyl residue acts as an internal nucleophile. The BF₃-complex 23 can undergo the ring enlargement to 25 by an intramolecular electrophilic aromatic substitution (Scheme 6). Alternatively, the ring-opening of 23 to the corresponding 1-azaallyl cation is conceivable, the latter being attacked by the phenyl ring to give 24. The decomplexation of 25 can occur by a reaction with fluoride ion, which has possibly been generated from BF₃ and traces of water. This could explain the formation of the tetrafluoroborate 19.

Although the hydrolysis of the tetrafluoroborate 19 to indolin-2-one 21 can be achieved by treatment with NaOH followed by refluxing in H₂O/THF, the procedure via the acetylated 22 gave more satisfying results. The latter was partly hydrolyzed during the washing of the chloroform solution with water, complete hydrolysis was achieved on treatment with aqueous HCl. It is likely that the intermediate 27 is formed which
leads to the product by elimination of acetamide (Scheme 7). On the other hand, the de-acetylation to 26 and subsequent hydrolysis of the amidine group cannot be excluded.

Conclusions

With the presented results, a novel ring enlargement reaction of N-phenyl-2H-azirin-3-amines has been established. This reaction, leading to 2-amino-2,3-dihydro-1,3,3-trimethylindolium tetrafluoroborate (19) opens a new access to 1,3,3-trisubstituted indolin-2-ones. Among a multitude of biologically active indole derivatives, compounds containing the indolinone ring system are very common, e.g. some cardiotonics [26, 27]. Furthermore, N-alkylated indolin-2-ones show adrenergic potentiating activity, and some antidepressant compounds were prepared from N-phenylindolin-2-ones as well as from N-phenylindolines [28]. Indolin-2-ones are also useful intermediates in alkaloid synthesis, e.g. the Calabar bean alkaloid [29] phystostigmin [30] (latest published syntheses [31] (racemic), [32] (enantioselective)) which is considered to be one of the first compounds to be recognized as an acetyl choline-blocking agent and is used clinically in the treatment of glaucoma [33].

Experimental Section

General

Thin-layer chromatography (TLC): Merck TLC aluminium sheets. Preparative TLC: Merck PLC plates (glass), silica gel 60 F254, 2 mm. Column chromatography (CC): Uetikon-Chemie Chromatographiegel C-560. High performance liquid chromatography (HPLC): Varian-590, Nucleosil 100–7; detection at λ = 254 nm. M.p. Mettler-FP-5 apparatus or Büchi 510 apparatus; uncorrected. IR Spectra: Perkin-Elmer-781 spectrophotometer or Perkin-Elmer-1600-FT-IR spectrophotometer; in KBr unless otherwise stated. 1H (300 MHz) and 13C NMR (75.5 MHz) Spectra: Bruker ARX-300 instrument; at 300 K; 13C signal multiplicity from DEPT spectra. MS: Finnigan SSQ-700 or MAT-90 instrument for CI.

2,2,3,N-Trimethyl-N-phenyl-2H-azirin-3-amine (1a) [21]

A solution of 2,2,N-dimethyl-N-phenylpropanamide (18) in CH2Cl2 was treated with COCl2 followed by HCl elimination using Et3N. The resulting 2-chloroenamine was purified by distillation, dissolved in diethyl ether (Et2O) and reacted with NaN3 to give 1a in 60–70% yield.

2-Amino-2,3-dihydro-1,3,3-trimethylindolium tetrafluoroborate (19)

To a stirred solution of 1a (484 mg, 2.4 mmol) in THF (60 ml) at −78 °C, BF3·OEt2 (0.63 ml of approx. 48% BF3 in Et2O, ca. 2.4 mmol) was added. Then, the solution was allowed to warm up slowly to ca. 23 °C, and stirred for 12 h. After addition of Et2O, a colorless precipitate was formed, which was filtered and recrystallized from ethanol (EtOH): 463 mg (68.6%) of 19; colorless crystals, m.p. 246.5–247.7 °C.

In an analogous experiment with 174 mg (1.0 mmol) of 1a in 25 ml of Et2O, a colorless precipitate was formed during the addition of ca. 1 mmol of BF3·OEt2 at −78 °C. After warming up to 23 °C, the mixture was stirred for 12 h, filtered, and the residue was recrystallized from EtOH to
give 214 mg (81.5%) of 19. IR (KBr): 𝜈 = 3390, 3136, 3240, 3200, 3160, 3100, 3040, 2960, 1695, 1680, 1615, 1505, 1470, 1430, 1370, 1355, 1305, 1260, 1205, 1120, 1080, 1030, 940, 865, 765, 740, 695, 660 cm⁻¹. 1H NMR (D₂O/MeSO): 𝜉 = 10.07 (s, NH), 9.77 (s, NH), 7.5 (d-like, 1 arom. H), 7.41 (t-like, 1 arom. H). 7.30 (d-like, 1 arom. H). 7.24 (t-like, 1 arom. H), 3.49 (s, CH₃N), 1.52 (s, 2 CH₃). 13C NMR (D₂O/MeSO): δ = 175.6 (s, N-C-N₂H), 141.2, 136.5 (2s, 2 arom. C), 128.4, 124.8, 122.4, 110.7 (4d, 4 arom. CH), 46.8 (s, C-3), 29.3 (q, CH₃N), 24.0 (q, 2 CH₂). CI-MS: m/z (%) = 175 (2, [M-BF₄]⁻), 159 (4). Analysis for C₁₁H₁₂N₂O₂ (262.05): calcd. C 50.42, H 5.77, Found: C 50.35, H 5.76, N 10.76.

2-Amino-2,3-dihydro-1,3,3-trimethylindolylidrahydrate (20)

A solution of 19 (100 mg, 0.38 mmol) in the least amount of water was cooled to 0 °C, and 10 ml of aqueous NaOH (30%) were added. The mixture was stirred for 20 min and extracted with CH₂Cl₂. The organic phase was washed with brine and dried over Na₂SO₄ to give 67 mg (92%) of 20 as a yellow oil. IR (film): 𝜈 = 3300, 3060, 2970, 2930, 2870, 1645, 1610, 1500, 1470, 1460 m, 1390 m, 1365 m, 1310 m, 1250 w, 1220 w, 1185 m, 1160 w, 1120, 1075 m, 1020 m, 1005 m, 940 m, 860 m, 780 w, 750 w, 700 m, 630 m cm⁻¹. 1H NMR (D₂O/MeSO): δ = 7.22–7.12, 6.89–6.79 (2m, 4 arom. H), 3.12 (s, CH₂N), 1.28 (s, 2 CH₃). 13C NMR (D₂O/MeSO): δ = 174.7 (s, N-C-N₂H), 144.6, 135.8 (2s, 2 arom. C), 127.5, 121.8, 119.9, 106.5 (4d, 4 arom. CH), 43.6 (s, C-3), 26.5 (q, CH₃N), 26.2 (q, 2 CH₂). 1H NMR (CDCl₃): δ = 7.17 (t-like, 1 arom. H), 7.08 (d-like, 1 arom. H), 6.88 (t-like, 1 arom. H), 6.66 (d-like, 1 arom. H), 3.19 (s, CH₂N), 1.29 (s, 2 CH₃). 13C NMR (CDCl₃): δ = 177.0 (s, N-C-N₂H), 144.4, 135.8 (2s, 2 arom. C), 127.7, 121.9, 120.0, 106.8 (4d, 4 arom.CH), 44.6 (s, C-3), 27.1 (q, CH₃N), 26.6 (q, 2 CH₂). CI-MS: m/z (%) = 176 (12), 175 (100, [M-NH₂]⁺ or [M-OH]⁺). Analysis for C₁₁H₁₀N₂O₂ (192.26): calcd. C 68.72, H 8.39, N 14.57, found C 68.40, H 8.29, N 14.18.

N-(2,3-Dihydro-1,3,3-trimethylindolyl-2-yliden)-acetamide (22)

To a solution of 19 (300 mg, 1.14 mmol) in pyridine (3 ml), acetic anhydride (Ac₂O, 3 ml) was added and the mixture was stirred at ca. 23 °C for 16 h. Then, the solvent was evaporated and the residue dissolved in CHCl₃, washed with H₂O and brine, and dried over Na₂SO₄. After filtration, evaporation and column chromatography (hexane/Et₂O 5:2), the two products were purified by means of HPLC (Nucleosil 100–7, hexane/ethyl acetate 10:3, 0.5 ml/min, 13 atm): 80 mg (37.0%) of 22 as colorless crystals, m.p. 61.8–62.1 °C. IR (KBr): 𝜈 = 3055, 2969, 2929, 2869, 1711, 1615, 1606, 1494, 1472, 1460, 1428, 1385, 1353, 1306, 1287, 1248, 1212, 1158, 1128, 1079, 1045, 1019, 1000, 947, 856, 802, 754, 709, 699 cm⁻¹. 1H NMR (CDCl₃): 7.25 (t-like, 1 arom. H), 7.15 (d-like, 1 arom. H), 7.03 (t-like, 1 arom. H), 6.81 (d-like, 1 arom. H), 3.20 (s, CH₂N), 2.29 (s, COCH₂), 1.51 (s, 2 CH₃). 13C NMR (CDCl₃): 181.8 (s, N-C=O), 165.8 (s, N-C=N), 143.0, 136.9 (2s, 2 arom. C), 127.7, 122.1, 121.5, 107.8 (4d, 4 arom. CH), 46.8 (s, C-3), 28.3, 27.3 (2q, COCH₂, CH₃), 25.9 (q, 2 CH₂). EI-MS: m/z (%) = 216 (34, M⁺), 215 (31), 201 (57), 186 (25), 175 (37), 160 (100).

As a minor compound, 40 mg (20.0%) of 2,3-dihydro-1,3,3-trimethylindolylidrahydrate (21) was obtained as colorless crystals, m.p. 49.7 °C (25–50 °C). IR (KBr): 𝜈 = 3060, 2960, 2920, 2860, 1720, 1615, 1495, 1470, 1460, 1380, 1375m, 1350, 1310, 1250, 1125, 1070, 1045, 1020, 940, 760, 745, 700 cm⁻¹. 1H NMR (CDCl₃): δ = 7.16 (t-like, 1 arom. H), 7.12 (d-like, 1 arom. H), 6.96 (t-like, 1 arom. H), 6.75 (d-like, 1 arom. H), 3.12 (s, CH₂N), 1.30 (s, 2 CH₃). 13C NMR (CDCl₃): (see [34]). Analysis for C₁₁H₁₀N₂O (175.23): calcd. C 75.40, H 7.48, N 7.99; found C 75.21, H 7.41, N 7.79.

Hydrolysis of 20 and 22. A solution of 20 (100 mg, 0.52 mmol) in H₂O/THF (1:1 v/v, 15 ml each) was refluxed for 3 days and extracted with Et₂O. The organic phase was washed with brine and dried over Na₂SO₄ to give 86 mg (94%) of 21. A solution of 22 (50 mg, 0.23 mmol) in 10% HCl in 5 ml was refluxed for 1 h and extracted with Et₂O. The organic phase was washed with aqueous NaHCO₃ solution, brine, and dried over Na₂SO₄ to give 37 mg (91%) of 21.

X-Ray crystal-structure determination of 19 and 22 (see Figs 1 and 2, Table 2) [35]. All measurements were made on a Rigaku AFC5R diffractometer using graphite-monochromated Mo–Kα radiation (λ = 0.71069 Å) and a 12 kW rotating anode generator. The data collection and refinement parameters are given in Table 2, and views of the molecules are shown in Figs 1 and 2. The intensities were corrected for Lorentz and polarization effects and, in the case of 19, an empirical absorption correction based on azimuthal scans of several reflections [36] was applied. Each structure was solved by direct methods using SIR 92 [37] for 19 and SHELXS 97 [38] for
Table 2. Crystallographic data for compounds 19 and 22.

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</tbody>
</table>

22, respectively, which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C-H) = 0.95 Å) and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 \(U_{eq}\) of its parent atom. Refinement of the structures was carried out on \(F\) using full-matrix least-squares procedures, which minimized the function \(\Sigma w(F_{o} - |F_{c}|)^{2}\). Corrections for secondary extinction were applied.

Neutral atom scattering factors for non-hydrogen atoms were taken from [39a], and the scattering factors for H-atoms were taken from [40]. Anomalous dispersion effects were included in \(F_{c}\) [41]; the values for \(f'\) and \(f''\) were those of [39b]. The values of the mass attenuation coefficients are those of [39c]. All calculations were performed using the teXsan crystallographic software package [42].

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[35] Crystallographic data (excluding structure factors) for the structures of 19 and 22 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-145098 and CCDC-145099. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-0) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).


[38] G. M. Sheldrick, SHELXS 97, Program for the Solution of Crystal Structures, University of Göttingen, Germany (1997).


