Cyclization of Nitroacetamide Derivatives with a Tethered Phenyl Ring in Triflic Acid

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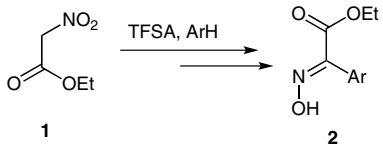
Received: 03.12.2013; Accepted after revision: 19.02.2014

This publication is dedicated to the memory of Professor Jean-Marie Coustard who supervised this work but passed away at the end of August 2013. Rest in peace dear Professor.

Abstract: *N*-(3-Hydroxypropyl)-2-nitro-*N*-(ω-phenylalkyl)acetamides underwent intramolecular cyclization in triflic acid to afford the corresponding hydroxyimino six- to nine-membered benzofused lactams. The six-membered derivative slowly transformed into 2-(3-hydroxypropyl)isoquinolin-3-one. NMR spectroscopic analysis in situ provided information on the cationic species involved in the reaction, permitting a mechanism to be postulated. This reaction provides a novel and simple route to benzofused lactams.

Key words: cations, protonation, cyclization, lactams, bicyclic compounds

Nitroacetic acid and its derivatives are useful molecules for the introduction of nitro groups when the nitration methodology is not satisfactory.[1] For instance, nitroacetamides are important precursors for the synthesis of isatins[2] and are used as a peptide synthons in the synthesis of dipeptides.[3]



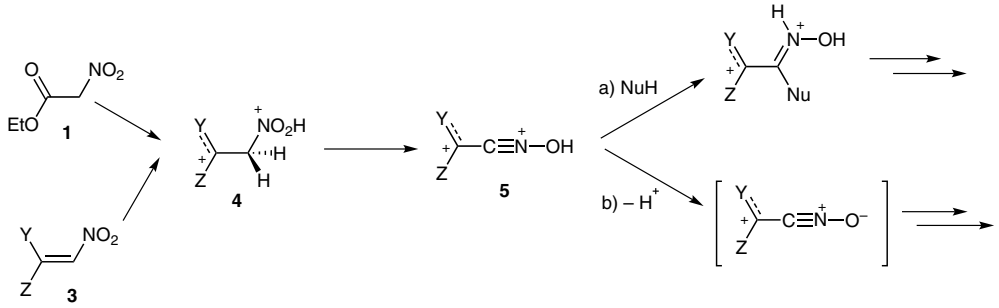
Scheme 1

In triflic acid or in $HF–SbF_5$, ethyl 2-nitroacetate (**1**) undergoes protonation and the loss of a molecule of water to afford a transient reactive hydroxynitrilium ion (protonated nitrile oxide) able to react with aromatics to form, for instance, ethyl (2*E*)-2-hydroxyimmino-2-phenylacetate (**2**, Ar = Ph; Scheme 1).[4]

The configuration of the oxime is indirect evidence of the existence of a reactive transient species with a CN triple bond.[5]

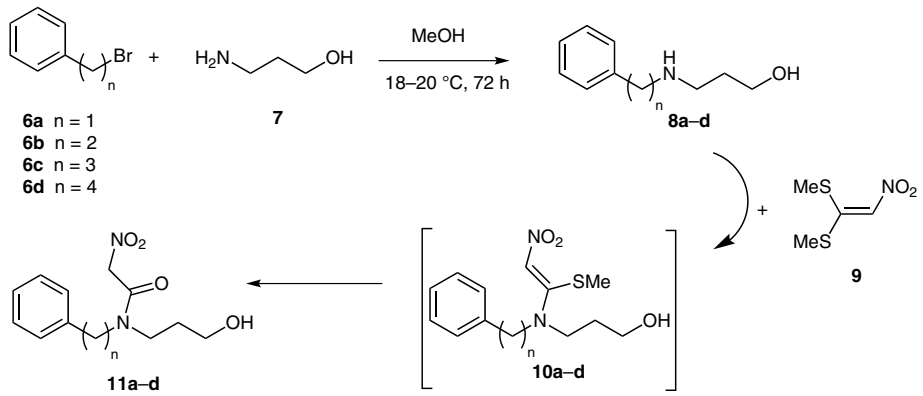
The protonation/dehydration of *N*,*S*- or *S*,*S*-nitroketene aminals **3** in triflic acid initially affords cations **4**, then the stable hydroxyiminium cations **5** that have been characterized by ^1H NMR and ^{13}C NMR spectroscopy at low temperature.[6,7] They are able to react in situ either with anions $F^–$ in $HF–SbF_5$[6] or $CF_3SO_3^–$ in triflic acid[8] or aromatic rings.[6–11] During the quenching of the acidic medium, they may either be trapped by MeSH or MeOH,[6] or form a very reactive nitrile oxide able to react with a phenyl ring by a cycloaddition process, to afford a conjugated cyclohexadiene (Scheme 2).[9]

From a synthetic viewpoint, ethyl 2-nitroacetate (**1**) is a versatile synthon for the preparation of nitroacetamides in a one-step reaction with amines.[12] Nitroacetamides can also be prepared from nitroketene *S*,*N*-acetals,[3,13] by ring transformation of 3,5-dinitro-2-pyridones,[14] by the reac-



Scheme 2

SYNLETT 2014, 25, 0969–0974
Advanced online publication: 24.03.2014
DOI: 10.1055/s-0033-1340960; Art ID: ST-2013-D1105-L



Scheme 3

tion of nitroacetic acid chloride with amines,[15a] and from α-bromoacetamide by nucleophilic bromide displacement with nitrite.[15b] Approaches involving ring opening followed by intramolecular cyclization of phenyl-substituted lactams or cyclization of β,γ-unsaturated amides in triflic acid have also been reported.[16]

In the present paper we report on the reactivity of N,N-disubstituted nitroacetamides possessing a tethered phenyl ring **11a**–**d** in triflic acid. Nitroacetamides **11a**–**d** were prepared by a one-pot reaction between the corresponding 3-(ω-phenylalkylamino)propan-1-ol and 1,1-bis(methylthio)-2-nitroethylene.[13a] The presence of the 3-aminopropanol group contributes to the stability of the cationic species formed in trific acid and to the final isolated products.

The reaction between 1-bromo-ω-phenylalkyl derivatives **6a**–**d** and two equivalents of 3-aminopropan-1-ol (**7**) in methanol afforded the 3-(ω-phenylalkylamino)propan-1-ols **8a**–**d**. In a second step, **8a**–**d** were condensed with 1,1-bis(methylthio)-2-nitroethene (**9**) in refluxing *tert*-butanol (Scheme 3) with DMAP, to afford nitroacetamides **11a**–**d** (Scheme 3).[13a]

Nitroacetamides **11a**–**d** were isolated by column chromatography on silica gel in low to medium yields (24–41%) as indicated in Table 1.

The amidic function of the nitroacetamide is planar in the solid state[17] and the partial CN double bond character of the amidic function leads to the existence of two *Z*- and *E*-isomers in solution[18a,b] as indicated by the two sets of signals in the NMR spectra ($CDCl_3$), with a ratio close to 1:1; although this ratio depends upon factors such as the nature of the solvent, acidity, substituents, and possible π-stacking.[18c]

In triflic acid, the starting materials **11a**–**d** were cleanly transformed after three hours at 60 °C (Scheme 4) with yields varying from 61–66% (Table 1) except for **11a** for which the reaction was more complex and afforded **12a** along with the corresponding isoquinolin-2-one **13**.

Products, **12a**–**d** and **13** result from an intramolecular cyclization with the loss of a molecule of water (Scheme 4). The reaction leads to a complex mixture when n = 1 because of the aromatization of the ring with the loss of the oxime group leading to **13** (Scheme 4).

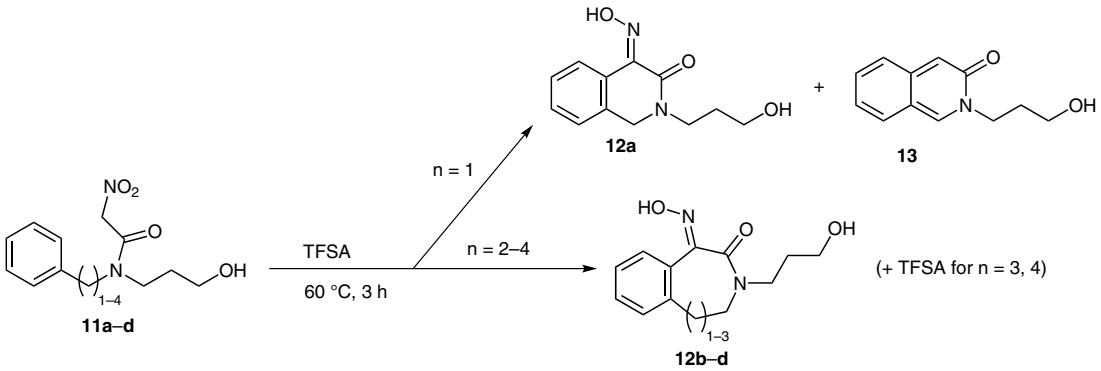
Compounds **12a**–**d** were characterized by the presence of four CH aromatic carbons (DEPT 135), an oxime carbon (δ_C = 154.7–162.7 ppm) and an amidic carbonyl carbon (δ_C = 162.9–169.7 ppm). The presence of a deshielded *ortho*-aromatic proton (δ_H = 8.9 ppm for **12a**) indicates the presence of an *E*-configured oxime, with the phenyl ring and the oxime OH in a *cis* configuration. The structures were further confirmed by X-ray crystallographic analysis of **12b** (Figure 1).[19–22] It is worthy of note that the primary alcoholic function was not affected during this reaction.

In the crystal, the nonaromatic ring is in a pseudo-boat conformation and the amidic function is planar. The torsion angle between the amidic C=O and the C=N oxime bonds is close to 68° and the torsion angle between the aromatic ring and the oxime is close to 60° causing only weak electronic conjugation in the benzazepinic system.

Table 1 Yields of Products **8**, **11**, **12**, and **13**

Starting compounds	Yield of products **8a**–**d** (%)[a]	Yield of nitroacetamide **11a**–**d** (%)[a]	Yield of bicyclic products **12a**–**d** and **13** (%)[a]
6a	44	28	6 + 11
6b	61	29	66
6c	51	41	61
6d	66	24	66

[a] Isolated yields after column chromatography.



Scheme 4

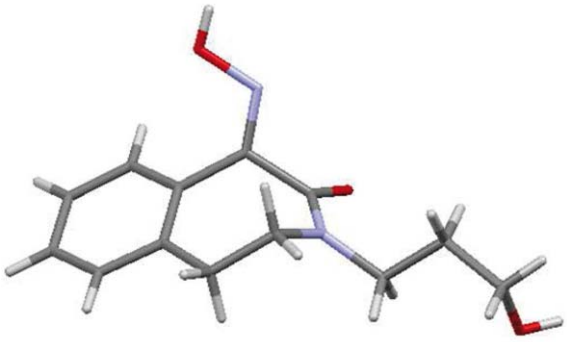


Figure 1 X-ray crystal structure of **12b**

To have a better understanding of the reaction mechanism, nitroacetamide **11b** in triflic acid was examined by NMR spectroscopy at 5 °C. Nitroacetamide **11b** was found to be protonated to give a stable trication at low or close to room temperature (molar ratio triflic acid/α-nitroacetamides **11** close to 56:1). Two isomeric cations **14a** and **14b** were formed as indicated by the two sets of NMR signals (*Z*/*E* ratio close to 2:1). Six CH_2 and three aromatic CH were identified by DEPT 135 analysis (Figure 2). Under these conditions the nitro group is known to be protonated but the proton is not observed because of its very rapid exchange rate with the medium.[23] The oxygen atom of the OH group is probably protonated as indirectly indicated by the deshielding of the methylene carbon bearing the alcohol (δ = 68.8 ppm as compared to δ_C = ca. 58 ppm in the nonprotonated form **11b**). The amide group is also known to be readily O-protonated in superacids[24a,b] and particularly in triflic acid where the DMF triflate salt can be isolated.[25] The major cationic species **14a** is proposed to be the *Z*-isomer due to the slight anisotropic magnetic shielding effect of the phenyl ring in this conformation[6–8] and because this places the tethered OH_2^+ further from the protonated nitro group. Given these assumptions, the probable structures of the cations **14a** and **14b** are given in Figure 2.

After 1.5 hours reaction time at 60 °C, cations **14a**,**b** were totally transformed into a stable cation **16b**, characterized by the presence of iminium and hydroxyiminium groups at δ_C = 159.7 and 151.1 ppm, respectively. Protonation of the alcoholic OH was not directly observed but can be postulated because of the strong deshielding of the methylene $CH_2OH_2^+$ (δ_C = 74.2 ppm as compared to δ_C = ca. 58.7 ppm in the starting compound **11b** and δ = 60.96 ppm in the final isolated product **12b**). Trication **16b** (Figure 3) is stable for weeks in triflic acid, the protonated alcoholic OH and the positively charged nitrogen at both ends of the alkyl chain appearing to have a stabilizing effect, in sharp

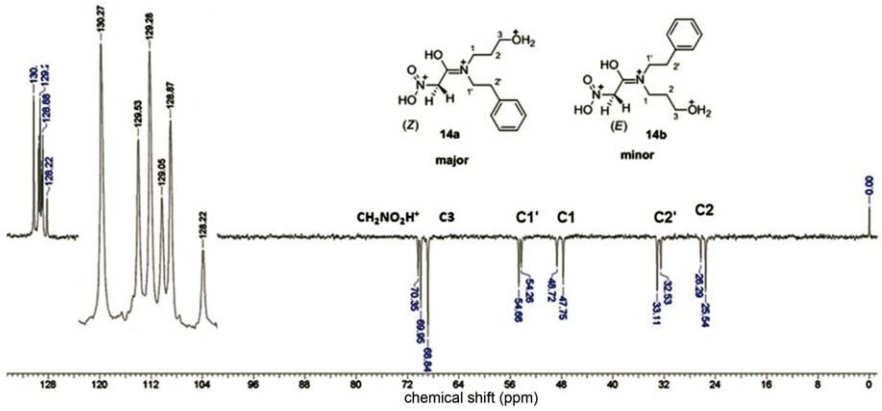


Figure 2 DEPT 135 NMR spectra of trications **14a** and **14b** in triflic acid at 278 K

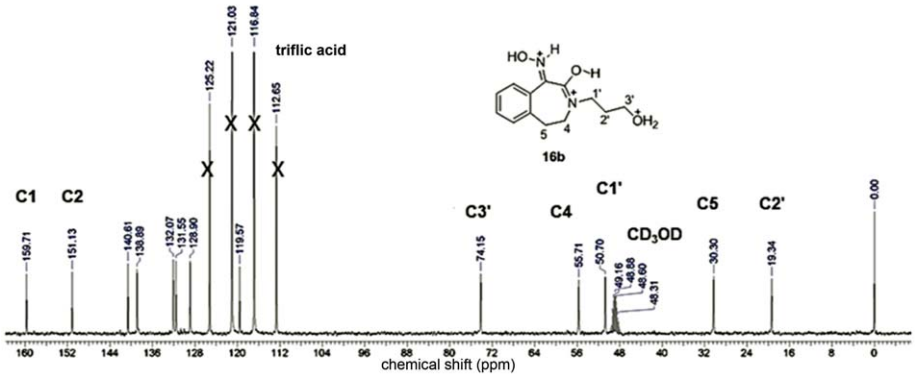


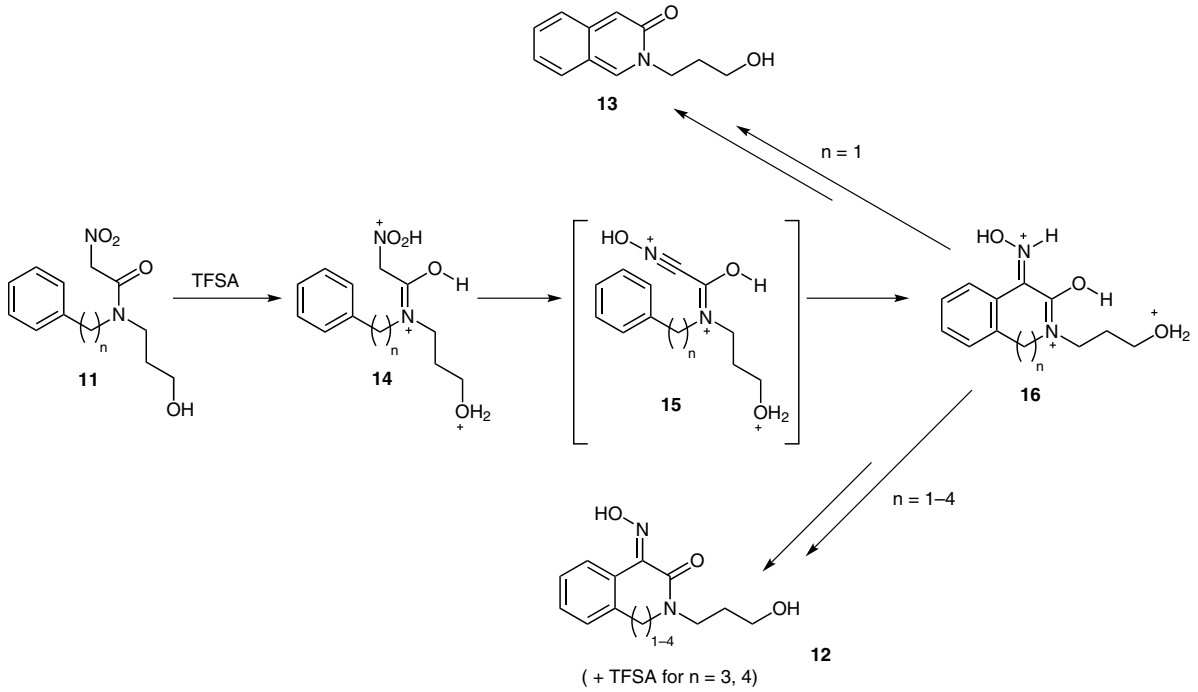
Figure 3 ^{13}C NMR spectrum of trication **16b** in triflic acid at 278 K

contrast to the degradation observed for long-chain aliphatic alcohols in superacid.[26] The high stability of N-protonated oxime has also been reported in triflic acid.[6–8,10,11] Protonation of the heteroatoms thus affords stable polyprotonated species **16b** insensitive to further electrophilic addition. Such a phenomenon has previously been proposed to explain the selective reactions on polyfunctionalized natural products in HF–SbF_5.[27]

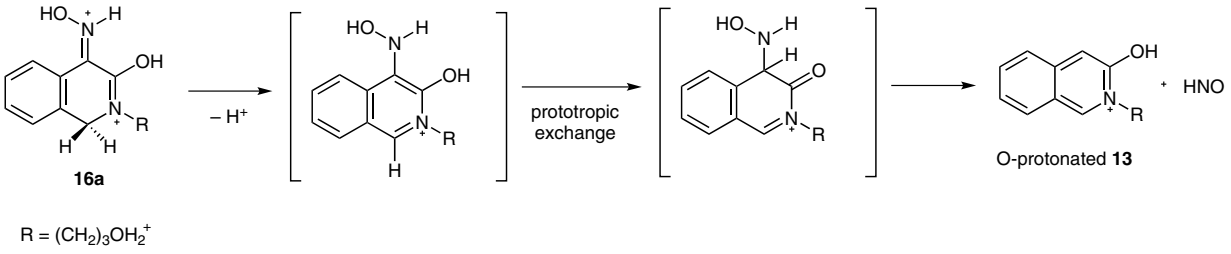
The mechanism in Scheme 5 for the formation of compounds **12** and **13** may be postulated. Substrate **11** undergoes multiple protonation and the loss of water to afford the conjugated hydroxynitrilium ion **15**. Once formed, **15** reacts with the tethered phenyl ring by electrophilic aromatic substitution to afford the observed trication **16b**, with the OH group of the formed oxime in the *cis* configuration relative to the aromatic ring, as described in Scheme 5. The oxime configuration is consistent with the mechanism of an addition on a triple bond, as predicted[5] and in agreement with previously reported results.[6–11] The mechanism also explains why only the *E*-configured trication **16** was formed. The sequence is completed by the involvement of other transient superelectrophilic species as postulated previously for reactions in triflic acid.[28]

On neutralizing the reaction, compounds **12** and **13** were isolated; compounds **12a**,**b** being isolated as neutral compounds, whilst **12c**,**d** were isolated as triflate salts.

The conformation of the nonaromatic ring is probably responsible for the increased basicity of the lactam because of the weak conjugation in the hydroxyimino benzofused lactam ring (nonplanarity). In favor of this assumption is the increased shielding of the aromatic proton close to the hydroxyimino group: δ_H = 8.88 ppm in **12a** (close to pla-



Scheme 5 Suggested mechanism for the formation of compounds **12** and **13**



Scheme 6

narity) to δ = 7.66 ppm in **12b** (θ ≈ 60° as indicated Figure 1). After several hours in methanol at room temperature, **12c**,**d** slowly isomerized to the *Z*-isomers. A plausible mechanism to explain the formation of **13** is illustrated in Scheme 6, wherein the trication **16a** would undergo deprotonation followed by prototropic exchanges leading to loss of the oxime, to afford the O-protonated isoquinolin-2-one **13**.

In conclusion, the present study extends previous works on the use of hetero-substituted nitroethene derivatives and 2-nitroesters in the field of heterocyclic synthesis. In triflic acid at 60 °C for three hours, nitroacetamides **11** lead to conjugated hydroxynitrilium ions which undergo an electrophilic aromatic substitution to afford the corresponding hydroxyimino-benzofused lactams (isoquinolinone, benzazepinone, benzazocinone, and benzazoninone). The six-membered ring hydroxyimino lactam slowly eliminates the oxime group to afford the corresponding isoquinolin-2-one. From a practical viewpoint, this reaction affords a simple route to benzofused lactams such as benzazocin-2-one and benzazonin-2-one derivatives that have been reported as potential angiotensin converting enzyme inhibitors, antihypertensive agents, and for the treatment of neuropsychological disorders.[29]

Typical Procedures

Synthesis of *N*-Benzyl-*N*-(3-hydroxypropyl)-2-nitroacetamide (11a)

1,1-Bis(methylthio)-2-nitroethylene (**9**, 1.00 g, 6.06 mmol) was added to a solution of *N*-benzylamino-3-propan-1-ol (**8a**, 1.00 g, 6.06 mmol) and DMAP (0.74 g, 6.06 mmol) in *t*-BuOH (20 mL). The resulting solution was heated to reflux for 24 h under nitrogen atmosphere monitoring by TLC (CH_2Cl_2–MeOH, 97:3). After cooling to r.t., the solvent was removed in vacuo to afford an oily residue that was purified by flash chromatography on silica (CH_2Cl_2–MeOH, 98:2) to give nitroacetamide **11a** (oil, 0.42 g, 28%) as a mixture of *Z*- and *E*-isomers in a ratio close to 1:1.

(*Z*)-*N*-Benzyl-*N*-(3-hydroxypropyl)-2-nitroacetamide [(*Z*)-11a]

^{1}H NMR(300 MHz, $CDCl_3$): δ = 1.77 (m, 2 H, $CH_2CH_2CH_2$), 3.28 (t, *J* = 6.7 Hz, 2 H, NCH_2CH_2), 3.62 (m, 2 H, CH_2OH), 4.49 (s, 2 H, CH_2Ph), 5.27 (s, 2 H, CH_2NO_2), 7.17–7.20 (m, 1 H, *p*-H), 7.24–7.43 (m, 4 H, arom. *o*-H and *m*-H). ^{13}C NMR (75 MHz $CDCl_3$): δ = 30.14 ($CH_2CH_2CH_2$), 43.42 (CH_2N), 51.64 (CH_2Ph), 59.20 ($HOCH_2$), 77.40 (CH_2NO_2), 126.53 (*p*-CH), 128.79 (*o*-CH), 129.79 (*m*-CH), 135.07 (*ipso*-C), 162.45 (C=O).

(*E*)-*N*-Benzyl-*N*-(3-hydroxypropyl)-2-nitroacetamide [(*E*)-11a]

^{1}H NMR(300 MHz, $CDCl_3$): δ = 1.77 (m, 2 H, $CH_2CH_2CH_2$), 3.62 (m, 4 H, NCH_2CH_2 and CH_2OH), 4.62 (s, 2 H, CH_2Ph), 5.58 (s, 2 H, CH_2NO_2), 7.17–7.20 (m, 1 H, arom. *p*-H), 7.24–7.43 (m, 4 H, arom. *o*-H and *m*-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.33 ($CH_2CH_2CH_2$), 44.36 (NCH_2CH_2), 48.72 (CH_2Ph), 58.26 (CH_2OH), 77.58 (CH_2NO_2), 128.22 (*p*-CH), 128.52 (*o*-CH), 129.19 (*m*-CH), 136.49 (*ipso*-C), 163.09 (C=O). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{16}N_2O_4$ + Na: 275.1008; found: 275.1005.

Synthesis of (1*E*)-1-Hydroximino-3-(3-hydroxypropyl)-4,5,6,7-tetrahydro-3-benzazonin-2-one (12d)

Nitroacetamide **11d** (294.00 mg, 1.00 mmol) was dissolved in triflic acid (5.00 mL, 56.20 mmol) at 2 °C under nitrogen (molar ratio triflic acid/α-nitroacetamides **11** ca. 6:1). The solution was stirred at 60 °C reaction was complete, monitoring by TLC (3 h). At the end of the reaction, the solution was cooled below 0 °C and then poured into 50 mL of CH_2Cl_2–MeOH (90:10) at –60 to –40 °C. The resulting solution was allowed to warm with gentle stirring and, when the temperature was close to 0 °C, cold brine (10.00 mL) and then anhydrous Na_2CO_3 (6.00 g) were added. The organic phase was separated, and the aqueous phase was further extracted with CH_2Cl_2–MeOH (90:10; 4 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residual oil was purified by column chromatography (CH_2Cl_2–MeOH, 95:5) to afford **12d** as its triflate (280.00 mg, 66%) as colorless crystals.

Mp 55.6 °C. IR (KBr): 3066 5 (s), 2951, 2866, 2363, 1734 (s), 1617 (m), 1459 (m), 1437 (m), 1275 (s), 1250 (s), 1170 (s), 1031 (s), 763 (m), 639 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (br s, 4 H, $CH_2CH_2CH_2C\leq$), 2.06 (q, *J* = 5.7 Hz, 2 H, CH_2CH_2OH), 2.69 (t, *J* = 6.3 Hz, 2 H, $CH_2C\leq$), 2.94 (m, 4 H, CH_2NHCH_2), 4.45 (br s, 2 H, CH_2OH), 7.16 (d, *J* = 7.5 Hz, 1 H, *o*-H), 7.31–7.45 (m, 3 H, arom. H). ^{13}C NMR (75 MHz, CD_3OD): δ = 24.27 ($CH_2CH_2CH_2C\leq$), 25.67 (CH_2CH_2OH), 26.18 ($CH_2CH_2C\leq$), 33.05 ($CH_2C\leq$), 43.87 ($CH_2CH_2CH_2OH$), 46.07 (CH_2N), 64.67 (CH_2OH), 122.11 (qd, $J_{C,F}$ = 318.4 Hz, $CF_3SO_3^-$), 127.93 (C-10), 129.94 (C-8), 130.88 (C-11), 131.09 (C-9), 132.52 (C-11a), 140.51 (C-7a), 151.64 (C=NOH), 165.33 (C=O). ^{19}F NMR (282 MHz, acetone-d_6): δ = –79.24 ($CF_3SO_3^-$). HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3$: 277.1552; found: 277.1556.

Acknowledgement

The authors thank CNRS/France for financial support, the 'Ministère des Affaires Etrangères' France, for Fellowship funds (S.S. and S.Y.) and the 'Ministère de l'Enseignement Supérieur' Ivory Coast (B.F.).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are full experimental details, representative ^{1}H and ^{13}C NMR spectra and X-ray data.

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(22) X-ray intensity data were collected on a Bruker X8-APEX2 CCD area-detector diffractometer using Mo Kα radiation (λ = 0.71073 Å). Three sets of narrow data frames (120 s per frame) were collected at different values of θ, for 1 and 2 initial values of φ and ω, respectively, using 0.5° increments of φ or ω. Data reduction was accomplished using SAINT V7.03.[20] The substantial redundancy in data allowed a semiempirical absorption correction (SADABS V2.10)[20] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELXTL V6.14.[21] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms. Crystal data, data collection, and processing parameters were deposited at the Cambridge Crystallographic Data Centre under the reference CCDC-875333.
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