A Simple and Efficient Synthesis of N-Substituted Cyclohex-3-enamines

Mónica Álvarez-Pérez,*[1] José Marco-Contelles*

Laboratorio de Radicales Libres y Química Computacional, IQOG (CSIC), C/ Juan de la Cierva 3, 28006 Madrid, Spain
Fax +34(91)3944103; E-mail: monicaap@quim.ucm.es; E-mail: iqoc21@iqog.csic.es

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Abstract: A straightforward preparation of N-substituted cyclohex-3-enamines starting from the commercially available *trans*-4-aminocyclohexanol hydrochloride is described. Cyclohex-3-enamino-functionalized compounds have proven to be interesting intermediates in medicinal chemistry. The method here described is cheaper, more scalable and tolerant of a broader variety of functional groups than those found in the literature for this type of compound.

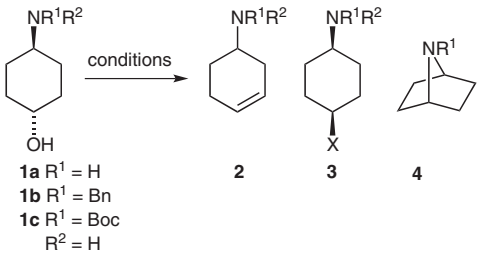
Key words: eliminations, olefinations, medicinal chemistry, amines, nitrogenated cyclohexenes

Cyclohexenes containing a nitrogen atom at the homoallylic position have proven to be useful intermediates for the synthesis of bicyclic heterocycles such as 7-azabicyclo[2.2.1]heptanes[2,3] or 6-azabicyclo[3.2.1]octanes.[4] Both are present in pharmacologically interesting alkaloids: the former in epibatidine,[5] the latter in azaprophen[6] and hetisine.[7]

Traditionally, cyclohexenes have been synthesized by Diels–Alder cycloadditions (DA), however, the DA approach requires the use of complex dienophiles[8] or subsequent rearrangement reactions[9] when a nitrogen atom at the 3-position is needed. Ring-closing-metathesis reactions (RCM) have been presented as an alternative to DA reactions for the synthesis of these interesting intermediates.[10] Nevertheless, high cost and problems in scaling-up are significant drawbacks for the use of RCM as a synthetic route to simple cyclohex-3-enamine derivatives.

We previously described the synthesis of epibatidine analogues[2] and, particularly, 7-azabicyclo[2.2.1]heptanes[11] using commercially available cyclohex-3-enecarboxylic acid as starting material.[3] However, because scaling up this sequence presented both technical difficulties and safety issues, it became necessary to develop a new protocol which reduced the cost of these useful compounds, was scalable without loss of efficiency and, very importantly, allowed the preparation of a broad variety of cyclohex-3-enamine derivatives starting from the same compound. We wondered if *trans*-4-aminocyclohexanol hydrochloride (**1a**·HCl) would be a suitable starting compound for our purposes.[12]

A large number of catalysts and reagents have been developed for olefin syntheses via alcohols.[13] Nevertheless, the presence of a nitrogenated moiety in a molecule can be expected to cause a decrease in selectivity as it may react with the reagent[4] and/or participate in a cyclodehydration process.[12,14] Bearing this in mind, a preliminary evaluation of conditions for the dehydration of compounds **1a–c** was carried out (Scheme 1, Table 1). Our first attempt, using phosphorus oxychloride ($POCl_3$) in pyridine to dehydrate **1a**·HCl (entry 1, Table 1)[15] gave a complex mixture, the analysis of which proved to be difficult. A similar result was observed when the same conditions were applied to *trans*-4-benzylaminocyclohexanol (**1b**; entry 2). It is interesting to note that when triethylamine was used instead of pyridine in the case of amine **1b**,[15] a 54% yield of the corresponding cyclodehydration product **4b**[12b] could be isolated (entry 3).



Scheme 1

We then decided to use the Boc protecting group and prepared *tert*-butyl-*trans*-4-hydroxycyclohexylcarbamate (**1c**).[16] When testing the $POCl_3$ in pyridine system in this case, the desired functionalized cyclohexene **2c**[3] was obtained, although in a moderate yield of 52% (entry 4). Thus, different dehydration conditions were investigated. Thionyl chloride ($SOCl_2$) was chosen and used first on compound **1b**.[15] In this case, the required functionalized cyclohexene **2b**[4] was isolated in 27% yield, together with 20% yield of *N*-benzyl-*cis*-4-chlorocyclohexylamine (**3b**; entry 5). When applying the same reagent to compound **1c**, triethylamine had to be used in order to avoid deprotection of the Boc-carbamate.[15] Unfortunately, significant decomposition was observed (entry 6). An additional attempt to prepare compound **2c** using $SOCl_2$ was performed as showed in entry 7; thus, *trans*-4-aminocyclohexanol (**1a**)[17] was treated with $SOCl_2$ in chloroform as previously for **1b** and, before work-up, Boc_2O and potassium carbonate were added to the mixture.[15] However, under these conditions, just 13% of **2c** could be isolated. The triphenylphosphine, iodine, and imidazole system[18] was then employed as an alternative. These conditions should

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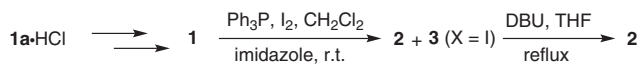
Table 1 Preliminary Evaluation of Conditions for Dehydration of *trans*-4-Amino-Functionalized Cyclohexanols

Entry	Starting material	Conditions	Product	Yield (%)[a]
1	**1a**·HCl	$POCl_3$, py	mixture	–
2	**1b**	$POCl_3$, py	mixture	–
3	**1b**	$POCl_3$, Et_3N	**4b**[12b]	54
4	**1c**[16]	$POCl_3$, py	**2c**[3]	52
5	**1b**	$SOCl_2$, $CHCl_3$, reflux	**2b**[4] + **3b** (X = Cl; 20%)	27
6	**1c**	$SOCl_2$, Et_3N	decomp.	–
7	**1a**[17]	1) $SOCl_2$, $CHCl_3$ 2) Boc_2O, K_2CO_3	**2c** + **1c** (10%)	13
8	**1c**	1) Ph_3P, I_2, imidazole 2) DBU, THF, reflux	**2c**	88

[a] After isolation.

work in a similar way to the $SOCl_2$ reagent in the sense of promoting a halogenation process, but the iodinated intermediate should more readily generate the desired elimination product. Moreover, the drawbacks resulting from the acidic media that built up during the transformation would be avoided under these conditions. Bearing this in mind, **1c** was treated with triphenylphosphine, iodine, and imidazole in dichloromethane obtaining a 1:1.5 mixture of olefin **2c** and iodinated derivative **3c** (X = I). After heating this mixture with DBU at reflux in tetrahydrofuran, we were delighted to see that **2c** was the only product remaining and was isolated in 88% yield (entry 8).[19] The sequence was then scaled up, with similar results.[20]

In view of the results presented in Table 1, two main conclusions can be drawn: firstly, chemoselectivity is low when starting from amines, no matter which conditions are used (entries 1–3, 5 and 7); secondly, when starting from carbamates, only the combination of triphenylphosphine, iodine, and imidazole and DBU and tetrahydrofuran THF was efficient (entries 4, 6 and 8). Following this last result, the scope of the dehydration of *trans*-4-amino-functionalized cyclohexanols under these conditions was investigated (Scheme 2, Table 2). Carbamate **1d**[4] provided not only the corresponding olefin **2d**[4] (entry 1, Table 2) but also the amine **2b**,[4] after removal of the Boc group (entry 2). Although deprotected amines did not give satisfactory results when used as starting materials, N-substituted cyclohex-3-enylamines can easily be obtained by using carbamate-protected starting materials and adding a deprotection step after dehydration. Amides also proved to be convenient functional groups for these reaction conditions (entries 3 and 4).[21,22] Finally, sulfonamides were also shown to be tolerant to the described conditions and no cyclization product was observed (entry 5).[12]



Scheme 2

Table 2 Reaction of *trans*-4-Amino-Functionalized Cyclohexanols with Triphenylphosphine, Iodine and Imidazole, and DBU

Entry	**1**	R^1	R^2	Product	Ratio (**2**/**3**)[a]	Yield (%)[b]
1	**1d**[4]	Bn	Boc	**2d**[4]	1:8.6	63
2	**1d**	Bn	Boc	**2b**	1:8.6	55[c]
3	**1e**[12b]	PhCO	H	**2e**	1.6:1	91
4	**1f**[23]	CF_3CO	H	**2f**[3]	1:1.2	69
5	**1g**[12a]	Ts	H	**2g**[24]	1.3:1	87

[a] Determined by ^1H NMR.
[b] Of isolated **2** after two steps from **1d**–**g**.
[c] After three steps from **1d**, including Boc-removal.

In summary, we herein present a method for the preparation of cyclohexenes bearing a nitrogenated functional group on the homoallylic position that formally consists of a dehydration process. Comparison to classical methods for dehydration in simple alcohols shows that the transformation does not occur satisfactorily under a broad variety of conditions. Starting materials and reagents needed are readily available and inexpensive and the procedure can easily be scaled up. Compared to other methodologies, the conditions described here allow the preparation of a broader variety of 3-nitrogenated cyclohexenes using the same starting material. The obtained products are potential intermediates in medicinal chemistry, which makes the methodology synthetically interesting and should make it the method of choice for the preparation of this type of compounds.

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous solvents (CH_2Cl_2, THF) were obtained by passing the solvent through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Flash column chroma-

tography was carried out using silica gel C60 (230 mesh) as the stationary phase. Analytical thin layer chromatography was performed on 0.25 mm thick precoated silica gel plates ($60F_{254}$). Compounds were visualized under UV light at 254 nm or by staining with either a 1% ninhydrin in EtOH solution or with cerium molybdate. ^{1}H NMR and ^{13}C NMR spectra were recorded at r.t. in $CDCl_3$, at 300, 400 or 500 MHz and at 75, 100 or 125 MHz, respectively, using solvent peaks [7.26 (H), 77.2 (C) ppm] as internal reference. The assignment of chemical shifts is based on standard NMR experiments (^{1}H, ^{13}C-DEPT, ^{1}H, ^{1}H-COSY, gHSQC, gHMBC). Melting points were determined on a microscope type apparatus and are uncorrected. Mass spectra and elemental analysis were carried out by the mass spectrometry services at CQO (CSIC, Spain).

Preliminary Evaluation of Conditions (Table 1)

Entry 1: Compound **1a**·HCl (152 mg, 1 mmol) was treated with pyridine (1.65 mL, 20.4 mmol) under argon at r.t. then $POCl_3$ (0.27 mL, 2.9 mmol) was added dropwise (the solution became cloudy). After stirring overnight, the reaction was diluted in CH_2Cl_2 (10 mL) and aq $CuSO_4$ (1 M, 5 mL) was carefully added. The layers were separated and the organic layer was washed with H_2O (2 × 10 mL), dried over Na_2SO_4, filtrated and evaporated. The resulting crude product was analyzed by TLC and ^{1}H NMR.

Entry 3: A solution of *trans*-4-hydroxycyclohexylamine hydrochloride (**1a**·HCl; 2.50 g, 16.5 mmol) in MeOH (226 mL) was treated with NaOH (0.1 M in MeOH, 40 mL, 4 mmol, 0.24 equiv) under argon at r.t. Molecular sieves (4 Å) and PhCHO (1.67 mL, 16.5 mmol, 1 equiv) were added (the solution became cloudy), followed by a solution of $NaBH_3CN$ (1.75 M in MeOH, 5.75 mL, 10.1 mmol, 0.61 equiv). 5 min after the end of the addition, a brown precipitate was observed. The reaction was stirred for 12 h, then the mixture was filtrated through Celite. The solid was washed with MeOH (3 × 100 mL) and the filtrate was treated with 1 M HCl until pH 1. Solvents were removed in vacuo and the resulting solid was redissolved in H_2O (200 mL) and extracted with Et_2O (3 × 100 mL). Layers were separated and the aqueous layer was basified with 1 N NaOH to basic pH, then extracted with CH_2Cl_2 (3 × 200 mL). The organic fractions were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting crude product was purified by flash column chromatography (MeOH–CH_2Cl_2, 0.5% then 1 → 2 → 4 → 8 → 10%), giving *trans*-4-(benzylamino)cyclohexanol (**1b**).

1b

Yield: 2.70 g (80%); crystalline colorless solid; mp 87–89 °C.

IR (KBr): 3266, 3153, 3064, 3036, 2925, 2856, 2833, 1454, 1368, 1100, 1065, 918, 893, 748, 734, 697, 639 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.12 (m, 5 H, ArH), 3.75 (s, 2 H, NCH_2), 3.55 (tt, *J* = 5.4, 3.3 Hz, 1 H, HCO), 2.45 (tt, *J* = 9.2, 2.8 Hz, 1 H, HCN), 2.00–1.81 (m, 4 H, 2 × CH_2), 1.80–1.58 (m, 2 H, NH, OH), 1.36–1.02 (m, 4 H, 2 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5 (C), 128.6, 128.2, 127.1, 70.5, 55.5 (CH), 51.5, 34.0, 31.2 (CH_2).

MS (ES): *m*/*z* (%) = 206.2/207.2/208.2 [M + H]$^+$.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.84; H, 9.30; N, 6.98.

Compound **1b** (108 mg, 0.53 mmol) in anhydrous CH_2Cl_2 (1.6 mL) was treated with Et_3N (0.08 mL, 0.54 mmol) under argon at r.t., then $POCl_3$ (0.05 mL, 0.54 mmol) was added dropwise (the mixture became slowly brown and warmed). After stirring overnight, the solvents were removed in vacuo and the crude product was purified by flash chromatography (MeOH–CH_2Cl_2, 2% + Et_3N 0.5%), to give several fractions in which only compound **4b**[12b] (54 mg, 0.29 mmol, 54%) could be identified.

Entry 5: Compound **1b** (62 mg, 0.3 mmol) was dissolved in $CHCl_3$ (8.2 mL) and $SOCl_2$ (1.4 mL, 19.2 mmol) was slowly added at r.t. The mixture was heated at reflux overnight, then the solvents were removed in vacuo and toluene was added and evaporated several times. The resulting crude material was treated with sat. aq K_2CO_3 (10 mL) and $CHCl_3$ (20 mL), the layers were separated and the organic layer was washed with sat. aq K_2CO_3 (3 × 10 mL), dried over $MgSO_4$, filtrated and evaporated. The colorless oil was purified by flash chromatography (MeOH–CH_2Cl_2, 1% then 2 → 3 → 5%) to isolate the olefin **2b**[4] as a colourless oil (15.2 mg, 0.081 mmol, 27%) and **3b**.

3b

Yield: 13.4 mg (20%); oil; R_f = 0.20 (MeOH–CH_2Cl_2, 5%).

IR (KBr): 3316, 2939, 2859, 1495, 1453, 1355, 1254, 1125, 736, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H, ArH), 4.36–4.27 (m, 1 H, HCCl), 3.83 (s, 2 H, NCH_2), 2.60 (ddd, *J* = 12.5, 7.6, 5.2 Hz, 1 H, HCN), 2.10–1.98 (m, 2 H), 1.87–1.66 (m, 6 H), 1.48 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9 (C), 128.7, 128.3, 127.1 (CH), 59.4, 54.4 (CH), 51.1, 32.8, 28.2 (CH_2).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}ClN$: 224.1201; found: 224.1204.

Entry 6: Compound **1c**[16] (65 mg, 0.3 mmol) was treated with Et_3N (8.2 mL) and $SOCl_2$ (0.6 mL, 8.23 mmol) was slowly added at r.t. After heating the mixture overnight at reflux, the excess of reagents was removed by distillation at normal pressure. The resulting black slurry was analysed by TLC and ^{1}H NMR: Decomposition was observed and no desired olefin was detected.

Entry 7: Compound **1a**[17] (162 mg, 1.4 mmol) was treated in $CHCl_3$ (38 mL) with an excess of $SOCl_2$ (6.5 mL) and the resulting mixture was then heated at reflux overnight. After cooling, the solvent and the excess of reagent were removed in vacuo and toluene was added and evaporated several times. The residue was suspended in a 1:1 mixture of $CHCl_3$–Et_3N (14 mL) and cooled to 0 °C. K_2CO_3 (387 mg, 2.8 mmol) and Boc_2O (315 mg, 1.7 mmol) were then added and the reaction was stirred for 11 h while reaching r.t. After this time, the reaction was diluted with $CHCl_3$ (20 mL) and sat. aq K_2CO_3 (20 mL) was added. Layers were separated and the organic layer was washed with sat. aq K_2CO_3 (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtrated and evaporated. The resulting crude material was purified by flash chromatography (EtOAc–hexane, 2.5 → 6 → 20 → 50%). Seven different fractions were obtained, in which only **2c**[3] (35.8 mg, 13%) and **1c**[16] could be identified (30.7 mg, 10%).

Dehydration with Ph_3P, I_2, Imidazole, and DBU; General Procedure

The corresponding *trans*-4-hydroxycyclohexylamino-derivative **1**, imidazole (2.12 equiv) and Ph_3P (3.41 equiv) were dissolved in anhydrous CH_2Cl_2 (12 mL/mmol of **1**) under argon. A freshly prepared solution of I_2 (2.06 equiv) in anhydrous CH_2Cl_2 (12 mL/mmol of **1**) was slowly added at r.t. and the mixture kept stirring overnight. H_2O (20 mL/mmol of **1**) and further CH_2Cl_2 (20 mL/mmol of **1**) were then added and the layers separated. The organic layer was washed with sat. aq $NaHCO_3$ (3 × 20 mL/mmol of **1**), 5% aq Na_2SO_3 (3 × 20 mL/mmol of **1**) and sat. aq NaCl (2 × 20 mL/mmol of **1**) and dried ($MgSO_4$). After removing solvents in vacuo, the residue was purified by flash chromatography to obtain a mixture of compounds **2** and **3**, which was directly used in the next step. When compounds **2** and **3** showed different R_f values, a small fraction of the mixture was re-purified in order to characterize the intermediate **3**.

The mixture of **2** and **3** was diluted in THF (3.2 mL/mmol of **3**) and DBU (1 equiv) was added. The mixture was refluxed for 18 h, then the solvent was removed in vacuo. The residue was re-dissolved in Et_2O (50 mL/mmol of **3**), treated with 1 M HCl (25 mL/mmol of **3**) and the layers were separated. The aqueous layer was extracted with additional Et_2O (4 × 50 mL/mmol of **3**) and the organic fractions were dried ($MgSO_4$) and filtered. Solvents were removed in vacuo, giving **2** with satisfactory purity.

N-Benzylated Compounds

Following the general procedure for dehydration, compound **1b** (94 mg, 0.46 mmol) gave a complex mixture from which only *N*-benzyl-7-azabicyclo[2.2.1]heptane[12b] (**4b**) could be identified (8 mg, 0.04 mmol, 9%).

tert-Butyl Benzyl(*trans*-4-hydroxycyclohexyl)carbamate (1d)[4]

A solution of **1b** (259 mg, 1.26 mmol) in $CHCl_3$ (2 mL) was cooled to 0 °C and Et_3N (0.18 mL, 1.26 mmol, 1 equiv), K_2CO_3 (0.35 g, 2.52 mmol, 2 equiv) and Boc_2O (0.285 g, 1.3 mmol, 1.03 equiv) were added. The mixture was stirred overnight while gradually warming to r.t. The precipitate was dissolved in H_2O (5 mL) and the mixture was diluted with additional $CHCl_3$ (5 mL). The layers were separated and the organic layer was washed with H_2O (3 × 10 mL), 1 M HCl (2 × 10 mL), 2 N NaOH (2 × 10 mL) and sat. NaCl (2 × 10 mL). After drying ($MgSO_4$), the organic fractions were filtered and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (MeOH–CH_2Cl_2, 2.5%), to give **1d** (302 mg, 79%).

Following the general procedure for dehydration, compound **1d** (224 mg, 0.74 mmol) gave a 1:8.6 mixture (191 mg, 64%) of *tert*-butyl-benzyl(cyclohex-3-enyl)carbamate[4] (**2d**) and *tert*-butyl benzyl(*cis*-4-iodocyclohexyl)carbamate (**3d**) after flash chromatography (EtOAc–hexane, 3 → 10%). Both compounds had the same R_f value. Reaction of 142 mg of the **2d**–**3d** mixture (0.32 mmol of **3d**, 0.35 mmol of **2d** + **3d**) with DBU (1 equiv), gave the olefin **2d** (100 mg, >99%) as a colourless oil.

2d–3d Mixture

Oil; R_f = 0.17 (EtOAc–hexane, 10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 48 H, ArH), 5.57 (s, 2 H, CH=CH), 4.75 (s, 8.6 H, HCl), 4.43 (br s, 20.2 H, HCN in **2d**, NCH_2 in **2d**, NCH_2 in **3d**), 4.18 (br s, 8.6 H, HCN in **3d**), 2.16–1.24 [m, 161.2 H, 3 × CH_2 in **2d**, 4 × CH_2 in **3d**, $C(CH_3)_3$ in **2d**, $C(CH_3)_3$ in **3d**].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 140.6 (C), 128.3, 126.7, 126.5, 125.6 (CH), 80.0, 79.8 (C), 54.0 (CH), 46.4, 35.9 (CH_2), 35.1 (CH), 29.8 (CH_2), 28.5 (CH_3), 27.1, 26.0 (CH_2).

tert-Butylcarbamates

Following the general procedure for dehydration, compound **1c** (1.08 g, 5 mmol) gave a 1:1.5 mixture (1.26 g, 92%) of *tert*-butyl-cyclohex-3-enylcarbamate (**2c**) and *tert*-butyl-*cis*-4-iodocyclohexylcarbamate (**3c**) after flash chromatography (EtOAc–hexane, 1% to separate excess Ph_3P and then EtOAc–hexane, 10% to obtain products). A part of this mixture (520 mg) was re-purified (EtOAc–hexane, 3 → 5%) to obtain olefin **2c** (138 mg, 37%) as a crystalline colorless solid and compound **3c** (338 mg, 55%). An additional fraction of the mixture (628 mg, 1.35 mmol of **3c**, 2.25 mmol of **2c** + **3c**) was further treated with DBU as described above, to give olefin **2c** (426 mg, 96%) as a colorless crystalline solid; mp 52–54 °C (Lit.[3] mp 52–54 °C).

3c

Crystalline colorless solid; mp 98–100 °C.

IR (KBr): 3299, 2969, 2936, 1680, 1533, 1365, 1322, 1276, 1256, 1229, 1177, 1162, 1044, 1017 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (br s, 1 H, HCl), 4.56 (br s, 1 H, NH), 3.54 (br s, 1 H, HCN), 2.14–1.99 (m, 2 H, 2 × C*H*HCHI), 1.89–1.55 (m, 6 H, 2 × CH*H*CHI, 2 × CH_2CHN), 1.43 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 79.4 (C), 48.2 (CH), 35.5 (CH_2), 33.4 (CH), 30.2 (CH_2), 28.5 (CH_3).

MS (EI): *m*/*z* (%) = 325.0/326.0/327.0 [M]$^+$.

Anal. Calcd for $C_{11}H_{20}INO_2$: C, 40.63; H, 6.20; N, 4.31. Found: C, 40.92; H, 6.35; N, 4.18.

N-Benzoylated Compounds

Following the general procedure for dehydration, compound **1e**[12b] (1.10 g, 5 mmol) gave a 1.6:1 mixture (1.15 g, 92%) of *N*-(cyclohex-3-enyl)benzamide (**2e**) and *cis*-*N*-(4-iodocyclohexyl)benzamide (**3e**) after flash chromatography (EtOAc–hexane, 6 → 25%). Part of it (415 mg) was re-purified (EtOAc–hexane, 10%) to obtain **2e** (186 mg, 56%) and **3e** (191 mg, 35%). An additional fraction of the mixture (602 mg, 0.92 mmol of **3e**, 2.40 mmol of **2e** + **3e**) was further treated with DBU as described above, to obtain olefin **2e**.

2e

Yield: 479 mg (99%); crystalline colorless solid; mp 114–116 °C.

IR (KBr): 3322, 3017, 2940, 1632, 1579, 1544, 1492, 1329, 718, 693, 656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.4 Hz, 2 H, ArH_o), 7.47 (t, *J* = 7.4 Hz, 1 H, ArH_p), 7.40 (t, *J* = 7.4 Hz, 2 H, ArH_m), 6.25 (br s, 1 H, NH), 5.76–5.69 (m, 1 H, C*H*=CH), 5.68–5.60 (m, 1 H, CH=C*H*), 4.37–4.26 (m, 1 H, HCN), 2.53–2.42 (m, 1 H, CH=CH-C*H*H-CH-N), 2.28–2.07 (m, 2 H), 2.06–1.89 (m, 2 H), 1.76–1.64 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 135.0 (C), 131.4, 128.6, 127.2, 127.0, 124.5 (CH), 45.0 (CH), 31.8, 28.0, 23.5 (CH_2).

MS (EI): *m*/*z* (%) = 201.1/202.1/203.1 [M]$^+$.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; O, 7.95. Found: C, 77.31; H, 7.46; N, 6.87.

3e

Crystalline colorless solid; mp 162–164 °C.

IR (KBr): 3435, 3285, 2949, 1630, 1535, 1492, 1342, 1328, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.74 (m, 2 H, ArH), 7.55–7.39 (m, 3 H, ArH), 6.16 (br s, 1 H, NH), 4.76 (s, 1 H, HCl), 4.20–4.00 (m, 1 H, HCN), 2.20–1.70 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 134.8 (C), 131.6, 128.7, 127.0, 47.7 (CH), 35.5 (CH_2), 33.6 (CH), 29.8 (CH_2).

MS (EI): *m*/*z* (%) = 329.0/330.0/331.0 [M]$^+$.

Anal. Calcd for $C_{13}H_{16}INO$: C, 47.43; H, 4.90; I, 38.55; N, 4.26. Found: C, 47.28; H, 4.79; N, 4.28.

N-Trifluoroacetylated Compounds

Following the general procedure for dehydration, compound **1f**[23] (135 mg, 0.64 mmol) gave rise to a 1:1.2 mixture (116.8 mg, 69%) of *N*-(cyclohex-3-enyl)-2,2,2-trifluoroacetamide[3] (**2f**) and *cis*-*N*-(4-iodocyclohexyl)-2,2,2-trifluoroacetamide (**3f**) after flash chromatography (EtOAc–hexane, 2 → 6%). Part of it (65.4 mg) was re-purified (EtOAc–hexane, 2 → 3 → 4%) to obtain **2f** (15.5 mg, 31%) and **3f** (38.9 mg, 46%). An additional fraction of the mixture (30 mg, 0.062 mmol of **3f**, 0.114 mmol of **2f** + **3f**) was further treated with DBU as described above, to obtain olefin **2f** (21.8 mg, 99%); mp 59–61 °C (Lit.[3] mp 59–60 °C).

3f
Crystalline colorless solid; mp 64–66 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.41 (br s, 1 H, NH), 4.73 (s, 1 H, HCI), 3.91 (m, 1 H, HCN), 2.28–1.60 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6 (d, *J* = 37.2 Hz, C), 115.9 (d, *J* = 288.1 Hz, C), 48.3 (CH), 35.2 (CH_2), 32.1 (CH), 28.9 (CH_2).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_8H_{12}F_3INO$: 321.9916; found: 321.9922.

***N*-Tosylated Compounds**
Following the general procedure for dehydration, compound **1g**[12a] (2.69 g, 10 mmol) gave a 1.3:1 mixture (2.81 g, 92%) of *N*-(cyclohex-3-ene)-*p*-toluenesulfonamide[24] (**2g**) and *N*-(*cis*-4-iodocyclohexyl)-*p*-toluenesulfonamide (**3g**) after flash chromatography (EtOAc–hexane, 10 → 25%). Both compounds showed the same R_f value. Reaction with DBU, starting from the **2g**–**3g** mixture (2.81 g, 3.98 mmol of **3g**, 9.15 mmol of **2g** + **3g**), gave olefin **2g** (2.18 g, 95%); mp 65–67 °C (Lit.[24] mp 65.8–67.0 °C).

2g–3g Mixture
Oil; R_f = 0.32 (EtOAc–hexane, 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 4.6 H, 2 × HC-C-S in **2g**, 2 × HC-C-S in **3g**), 7.27 (d, *J* = 8.2 Hz, 4.6 H, 2 × *H*C-C-Me in **2g**, 2 × *H*C-C-Me in **3g**), 5.61–5.53 (m, 1.3 H, C*H*=CH), 5.43 (dtd, *J* = 5.7, 4.5, 2.2 Hz, 1.3 H, CH=C*H*), 5.37 (d, *J* = 6.9 Hz, 1 H, NH in **3g**), 5.27 (d, *J* = 7.8 Hz, 1.3 H, NH in **2g**), 4.48 (br s, 1 H, HCI), 3.45–3.33 (m, 1.3 H, HCN in **2g**), 3.21 (br s, 1 H, HCN in **3g**), 2.39 (s, 6.9 H, Me in **2g**, Me in **3g**), 2.20–2.09 (m, 1.3 H, N-CH-*H*HC-HC=CH), 2.07–1.92 (m, 4.6 H, HC=CH-CH_2-CH_2, 2 × C*H*H-CH-I), 1.84 (dqd, *J* = 16.0, 5.4, 2.7 Hz, 1.3 H, N-CH-H*H*C-HC=CH), 1.76–1.67 (m, 1.3 H, HC=CH-CH_2-C*H*H), 1.67–1.56 (m, 6 H, 2 × CH*H*-CH-I, 2 × N-CH-CH_2 in **3g**), 1.55–1.43 (m, 1.3 H, HC=CH-CH_2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 143.2, 138.2, 138.1 (C), 129.7 (2 × CH), 126.9 (3 × CH), 124.0, 50.9, 49.0 (CH), 35.0, 32.3 (CH_2), 31.6 (CH), 30.8, 28.8, 23.6 (CH_2), 21.6 (2 × CH_3).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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