Increasing the N–H Acidity: Introduction of Highly Electronegative Groups into the Hydrazine Molecule

Aleksei Bredikhin,[a] Olga Tšubrik,[a] Rannar Sillard,[b] Uno Mäeorg*[a]

[a] Institute of Organic and Bioorganic Chemistry, University of Tartu, Jakobi 2, 51014 Tartu, Estonia
Fax +372(7)375245; E-mail: uno.maeorg@ut.ee

[b] Department of Medical Biochemistry and Biophysics, Karolinska Institutet, 171-77 Stockholm, Sweden

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Abstract: Various hydrazine derivatives containing combinations of trifluoroacetyl, trifluoromethanesulfonyl, and 2,4-dinitrophenyl groups were prepared. Synthetic strategy is studied in terms of using protecting groups and direct acylation.

Key words: acylations, hydrazines, neighboring-group effects, protecting groups, sulfonamides

Modern synthesis enables the attachment of different substituents to the hydrazine skeleton, thus allowing design of compounds with predetermined properties.[1,2] Contrary to common aryl-, alkyl- and acyl-substituted hydrazines, there are only few studies concerning derivatives which bear highly electronegative substituents.[3] Fluorinated imides have found usage in fuel cells and as components in solid polymer electrolyte systems.[4] In the same way, similar class of hydrazine derivatives potentially possess unusual electrochemical properties. Introduction of trifluoromethanesulfonyl group might have positive effect on the biological activity of hydrazine-based pharmaceuticals: firstly, it increases the solubility, secondly, the triflyl-containing analogues were found to inhibit carbonic anhydrases.[5] Also, derivatized hydrazines can be used as precursors of the amines with different substitution pattern, as trifluoroacetyl-activated N–N bond is easily cleaved by SmI_2.[6]

The correlation between acidities of hydrazine and similarly substituted ammonia derivatives can be useful in prediction of the potential of the compounds for the Mitsunobu-type alkylations, etc.[7] Recently, quantum chemical calculations afforded the pK_a of 1,1,2-tris(triflyl)hydrazine to be about 0.4 in DMSO, which reaches that of sulfuric acid.[8] Obviously, NH acids of this type could be of high interest for synthetic chemists as well. In order to determine pK_a values experimentally, we have started to develop a general synthetic approach to this kind of compounds, testing the extent of substitution to which the protecting groups strategy can be readily applied.[2]

Our work was aimed at the introduction of CF_3CO substituent in different combinations as shown in Scheme 1. One may think that di-, tri- and tetrasubstituted compounds are accessible via subsequent acylation of hydrazine. However, only symmetrical 1,2-bis(trifluoroacetyl)hydrazine (**1**) was obtained this way and the reported procedures are based on the use of anhydrous hydrazine (which is explosive and prohibited in many states for now) or afforded contaminated product.[3c,9] Tris(trifluoroacetyl)hydrazine was never described earlier. Tetrakis(trifluoroacetyl)hydrazine was presumably isolated by Young from 0.14 mol scale time-consuming reaction, carried out in a bomb between Hg salt of the compound **1** and trifluoroacetylanhydride.[3c] Structure of the product was not confirmed and thus the process is unsuitable as an example of modern synthetic technique.

In our studies, direct derivatization of electron-deficient **1** using standard acylation procedure $(CF_3CO)_2O$/DMAP/MeCN was found to be impossible. Therefore, the compounds **2** and **3** were obtained by stepwise deprotonation with *n*-BuLi and subsequent acylation with $(CF_3CO)_2O$ or CF_3COCl. The last reagent can be easily prepared by adding trifluoroacetic anhydride dropwise to pyridinium chloride;[10] the resulting gas was passed directly into the solution of Li salt of **1** or **2**.[11] After evaporation of solvents, crude products **2** (85% yield) and **3** (40%) were subjected to NMR and MS analysis. Magnetic inequivalence of the CF_3CO groups and C–F splitting causes the appearance of two CF_3 quartets in the ratio of 1:2 (the same goes for carbonyl signals) in the ^{13}C NMR spectrum of **2**. Under the same circumstances, ^{13}C NMR spectrum of **3** contains only one CF_3 quartet. Attempts to purify **2** by sublimation in vacuo induced its decomposition and formation of $CF_3CONHNHCOCF_3$ (most probably due to the disproportionation).

Previously published synthesis of **5c** employ either a multistep synthesis with hydrazinolysis on its end,[3b] harsh reaction conditions or anhydrous hydrazine as a reagent.[8,12] A recent study has also demonstrated instability of this compound and its disposition towards disproportionation.[13] Our synthesis started with compounds **4a** and **4b** which were easily obtained in 96–100% yields by reacting Boc- and Z-protected hydrazines with trifluoroacetic anhydride in MeCN or CH_2Cl_2.[14] Depending on what protecting group we chose to use (Cbz or Boc), either $CF_3CONHNH_2$ as a free base **5c** (94% yield) or salts **5a** and **5b** (78% and 100% yields) were obtained (ESI-HRMS: *m/z* calcd for $C_2H_4F_3N_2O$: 129.0276: found: 129.0270 $[MH]^+$). Contrary to the substance **5c**, the

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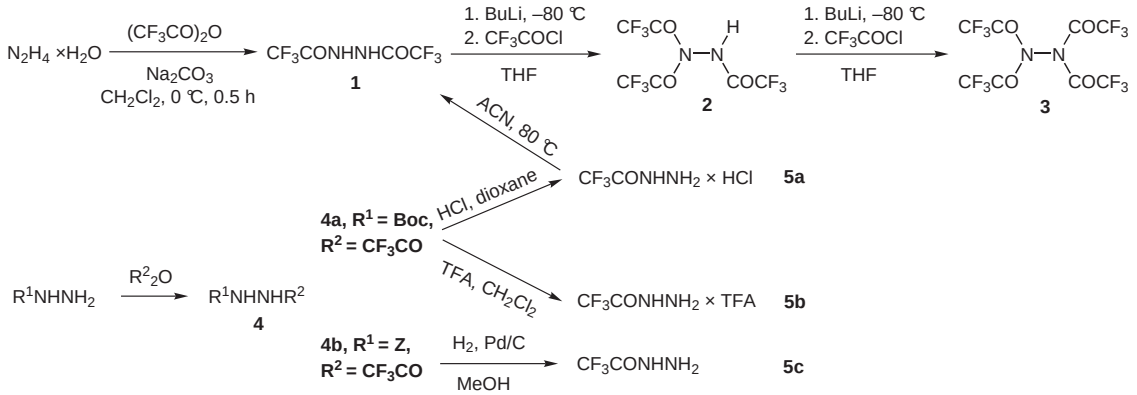

Scheme 1 Synthesis of trifluoroacetyl-substituted hydrazines

corresponding salts **5a** and **5b** are perfectly stable on storage at room temperature and the disproportionation was observed only when compounds were refluxed in acetonitrile ($CF_3CONHNHCOCF_3$ was formed). In analogy with typical amine salts, **5a** and **5b** can be employed in the synthesis or pK_a measurements.

An attempt to introduce more trifluoroacetyl groups into the compound **4a** under typical acylating conditions [$(CF_3CO)_2O/Et_3N$/DMAP] has failed. Instead of the desired compounds we have isolated $CF_3COCH{=}CHNEt_2$ (structure confirmed by ^1H NMR and ^{13}C NMR) as the only product due to the oxidation of triethylamine with $(CF_3CO)_2O$.[15] Attempted direct triacylation of $BocNHNH_2$ under the same conditions also has failed due to the same oxidation process [$(CF_3CO)_2C{=}CHNEt_2$ isolated and characterized by NMR].

Similarly with the compounds **4a** and **4b**, other combinations of different electron-withdrawing groups should be considered as derivatives with remarkable acidic properties. The disubstituted substances **4,** prepared in the current study, are demonstrated in Table 1 below.[16]

The obtained compounds are now being employed in the pK_a measurements. As it could be anticipated from high electron-withdrawing effect, pK_a of **1**, **4a** and **4c** reached values of 7–10 units (DMSO).[8]

Table 1 Disubstituted Hydrazines

Number	R^1	R^2	Conditions	Yield (%)
4a	Boc	$COCF_3$	0 °C, TEA, MeCN	96
4b	Z	$COCF_3$	0 °C, CH_2Cl_2	100
4c	Boc[a]	SO_2CF_3	–80 °C, TEA, CH_2Cl_2	63
4d	Z	SO_2CF_3	–80 °C to r.t., TEA, CH_2Cl_2	68
4e	DNP[b]	$COCF_3$	0 °C, TEA, CH_2Cl_2/ACN	98

[a] Previously prepared by Hendrickson.[17]
[b] 2,4-Dinitrophenyl.

In conclusion, this work reports novel systematic study of the preparation of multisubstituted hydrazines with several electronegative groups using trifluoroacetyl moiety as an example. All procedures reported here are characterized by easy reproducible techniques, mild reaction conditions, fast reactions and good yields. Neither extremely toxic compounds nor explosives have been used. From the strategical point of view, one does not have to use protecting groups for the directly accomplishable di-, tri- and tetrasubstituted derivatives, although activation of NH by metallation is absolutely essential. However, the protecting groups like Z and Boc are useful in the convenient preparation of monosubstituted derivative.

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(11) An oven-dried flask was charged with 224 mg of the compound **1** (1 mmol), then evacuated and backfilled with argon. Then, 8 mL of Et_2O was added to dissolve the solid and the solution was cooled down to –80 °C. A 1.6 M solution of *n*-BuLi in hexane (2 equiv, 1.26 mL) was added dropwise and the obtained mixture stirred for 30 min. In the other flask, 6 mL of trifluoroacetylanhydride was added to the solution of pyridinium chloride (10 equiv) in minimum quantity of TFA. The emerging gaseous CF_3COCl was passed into the solution of metallated compound **1**. The mixture was stirred for 30 min at –80 °C and then let to warm up to r.t. LiCl was filtered off and solvents were evaporated in vacuo, yielding 271 mg of **2** (mp 148–150 °C). The ESI molecular ion does not exist due to the rapid decomposition to **1**. ^{13}C NMR (DMSO-d_6): δ = 116.1 (q, J_{CF} = 286 Hz, CF_3CONH), 117.1 [q, J_{CF} = 294 Hz, $(CF_3CO)_2N$], 155.8 (q, J_{CF} = 37 Hz, CF_3CONH), 159.2 [q, J_{CF} = 33, $(CF_3CO)_2N$]. Compound **3** was obtained in the same way in THF using 1 equiv *n*-BuLi for the first deprotonation of **1**. After the reaction with CF_3COCl the addition of 1 equiv *n*-BuLi and CF_3COCl was repeated. THF was removed using rectification, furnishing **3** as a colorless oil. ESI-HRMS: *m/z* calcd for $C_8HF_{12}N_2O_4$: 416.9739; found: 416.9745 $[MH]^+$. ^{13}C NMR (DMSO-d_6): δ = 116.9 [q, J_{CF} = 293 Hz, $(CF_3CO)_2N$], 160.2 [q, J_{CF} = 34, $(CF_3CO)_2N$].
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(14) Compound **4a**: mp 130–132 °C. ^{1}H NMR (DMSO-d_6): δ = 1.42 (s, 9 H, Boc), 9.31 (s, 1 H, NH), 11.27 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ = 27.9 (Me, Boc), 80.1 (C_q, Boc), 115.9 (q, CF_3, J_{CF} = 287 Hz), 154.4 (CO, Boc), 156.2 (q, CF_3CO, J_{CF} = 36 Hz). IR: 3294, 3192 (NH), 1740, 1696 (C = O) cm^{-1}. Anal. Calcd for $C_7H_{11}F_3N_2O_3$: C, 36.85; H, 4.86; N, 12.28. Found: C, 37.14; H, 4.77; N, 12.03. Compound **4b**: mp 106–108 °C. ^{1}H NMR ($CDCl_3$): δ = 5.150 (s, 2 H, $PhCH_2$), 4.341 (s, 5 H, CH_{arom}), 9.096 (s, 1 H, NH-Z), 10.926 (s, 1 H, $NHCOCF_3$). ^{13}C NMR ($CDCl_3$): δ = 67.4 ($PhCH_2$), 116.0 (q, J_{CF} = 286 Hz, CF_3), 128.1, 128.3, 128.5, 136.0 (C_{arom}), 155.8 (CO, Z), 157.1 (q, J_{CF} = 38 Hz, CF_3CO). ESI-MS: *m/z* calcd for $C_{10}H_8F_3N_2O_3$: 261.049; found: 261.096 $[M^-]$.
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(16) Compound **4d**: mp 140–141 °C. ^{1}H NMR (DMSO-d_6): δ = 5.15 (s, 2 H, $PhCH_2$), 7.38 (s, 5 H, Ph), 10.12 (s, 1 H, NH-Z), 11.66 (s, 1 H, $NHSO_2CF_3$). ^{13}C NMR (DMSO-d_6): δ = 66.9 (s, $PhCH_2$), 119.2 (q, J_{CF} = 321 Hz, CF_3SO_2), 127.9, 128.2, 128.4, 136.0 (C_{arom}), 156.1 (CO). ESI-MS: *m/z* calcd for $C_9H_8F_3N_2O_4S$: 297.016; found: 297.083 $[M^-]$. Compound **4e**: mp 161–163 °C. ^{1}H NMR (DMSO-d_6): δ = 7.29 (d, J_{CH} = 9.6 Hz, 1 H, Ar), 8.39 (m, 1 H, Ar), 8.90 (d, J_{CH} = 2.6 Hz, 1 H, Ar), 10.41 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ = 115.1 (C_{arom}), 115.9 (J_{CF} = 286 Hz, $COCF_3$), 123.1, 130.5, 137.6, 147.1 (C_{arom}), 156.4 (J_{CF} = 36 Hz, CO). ESI-MS: *m/z* calcd for $C_8H_4F_3N_4O_5$: 293.013; found: 293.071 $[M^-]$.
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