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Stereochemistry and mechanism of oxidative 1,4-addition of trifluoroacetamide to 2,3-dimethylbuta-1,3-diene

Vera V. Astakhova, Mikhail Yu. Moskalik, Irina V. Sterkhova and Bagrat A. Shainyan*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: bagrat@irioch.irk.ru

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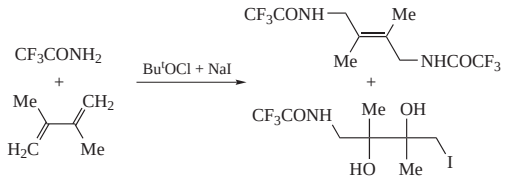
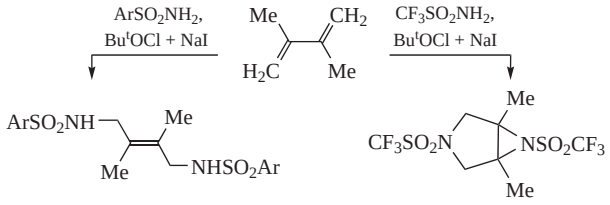
Oxidative addition of trifluoroacetamide to 2,3-dimethylbuta-1,3-diene leads to *N*,*N*′-[(2*E*)-2,3-dimethylbut-2-ene-1,4-diyl]-bis(trifluoroacetamide) and [(2*RS*,3*SR*)-*N*-(2,3-dihydroxy-4-iodo-2,3-dimethylbutyl)trifluoroacetamide. A tentative mechanism is proposed.



Oxidative amination of dienes is a route to their functionalization allowing one to prepare alkenes with two electronegative groups. Oxidative addition of amides or sulfonamides to butadienes was accomplished in the copper(II)-mediated reaction with saccharin,[1] or using iodobenzene diacetate in the reaction with sulfonimides,[2] or by addition of *N*-alkoxy-*N*-chloroureas[3] or *N*,*N*′-dibenzyloxyurea[4] to 1,3-dienes. The osmium-catalyzed aminohydroxylation of stilbenes, methyl *trans*-cinnamate and cyclohexene with chloramine-T,[5–7] as well as the catalytic asymmetric amidohydroxylation of *trans*-alkenes with sodium or lithium salts of *N*-bromoamides[8–10] are also worthy of note.

The products of oxidative amination, as distinct from the products of hydroamination, contain (besides the amido or sulfonamide group) a second electronegative substituent, like OH, halogen or the second amido moiety (*vide infra*). This may be an advantage of oxidative *versus* catalytic amination if further functionalization of the product is assumed.

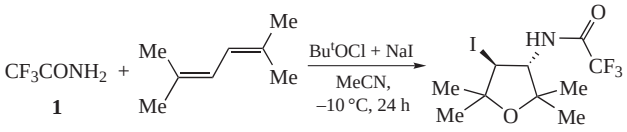
The behaviour of fluorinated amides and sulfonamides in the reactions of oxidative addition can differ from that of non-fluorinated analogues. Thus, triflamide shows a specific behaviour in reactions with alkenes[11,12] in the Minakata's oxidative system (Bu^{t}OCl + NaI) as compared to other sulfonamides.[13] Oxidative addition of triflamide and arenesulfonamides to dienes also affords different products.[14–16] For example, the reaction of 2,3-dimethylbuta-1,3-diene with triflamide gave the product of bicyclization of 3,6-diazabicyclo[3.1.0]hexane type, while with arenesulfonamides only linear products of 1,4-bis(arenesulfamidation) were obtained[14] (Scheme 1).



Scheme 1

With 1,5-hexadiene, triflamide gives the products of mono- and diheterocyclization,[15] whereas only the isomeric monoheterocyclization products are formed with arenesulfonamides.[16]

Nonfluorinated amides on treatment with the Minakata's oxidative system react with alkenes to afford substituted 4,5-dihydro-1,3-oxazoles.[17] In the same system, trifluoroacetamide **1**, as we recently showed, gave with alkenes and dienes a large diversity of products depending on the structure of the substrate.[18] In particular, with 2,5-dimethylhexa-2,4-diene *trans*-trifluoro-*N*-(4-iodo-2,2,5,5-tetramethyltetrahydrofuran-3-yl)acetamide was formed by addition–cyclization sequence[18] (Scheme 2).

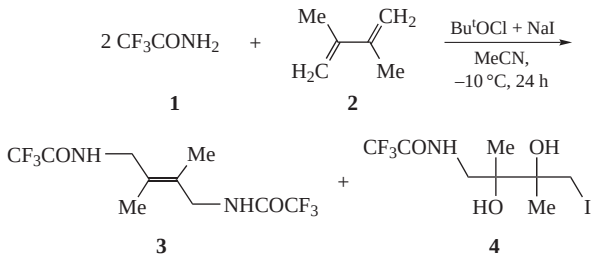


Scheme 2

In continuation of these studies and with specific behaviour of fluorinated amides in mind, we tried the reaction of trifluoroacetamide **1** with 2,3-dimethylbuta-1,3-diene **2** in a hope to obtain heterocyclic products, like in the reactions of dienes with trifluoromethanesulfonamide.[14]

However, the reaction of equimolar amounts of diene **2** and amide **1** at –10 °C proceeded with 79% conversion and the only isolated product was *N*,*N*′-[(2*E*)-2,3-dimethylbut-2-ene-1,4-diyl]-bis(trifluoroacetamide) **3**, which is similar to the product of the reaction between diene **2** and arenesulfonamides (*vide supra*). The reaction was accompanied by heavy resinification, so the yield was as low as 10% and could not be raised by variation of the temperature or the ratio of the reagents (Scheme 3).†

† Melting points were determined on a Boetius Block apparatus (VEB Analytik) and are uncorrected. IR spectra were taken on a Varian 3100 FT-IR or Bruker Vertex 70 spectrophotometer in KBr. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX 400 spectrometer at working frequencies 400 (^{1}H), 100 (^{13}C), 40 (^{15}N) and 376 (^{19}F) MHz in CD_3CN; ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield to TMS, ^{19}F NMR in ppm downfield to $CFCl_3$. ^{15}N NMR chemical shifts were obtained from 2D{^{1}H–^{15}N} spectra recorded by the use of a gradient probe working in the *hmbcgp* mode optimized to the long-range coupling constant J_{NH} of 9 Hz, and are reported in ppm downfield to $MeNO_2$. Elemental analyses were done on a Thermo-Finnigan Flash EA analyzer. All solvents were dried and purified before use according to



Scheme 3

The symmetrical structure of compound **3** is proved by the presence of only one set of signals in the ^{1}H and ^{13}C NMR spectra and one signal in the ^{19}F NMR spectrum. Ultimately, the structure of compound **3** was determined by X-ray analysis which revealed stereoselective formation of only the *E*-isomer of the product (Figure 1).‡ The molecule possesses the center of symmetry and has two S_2 rotoreflection axes passing through the center of the C=C bond and perpendicular to it.

The aforementioned $CuBr_2$-catalyzed oxidative sulfamidation of buta-1,3-dienes with saccharin also gives *trans*-1,4-adducts,[1] which can be considered as structural analogues of compound **3**, while with *N*,*N*′-dibenzyloxyurea diene **2** reacts *via* the oxidative *cis*-diamination route.[4]

By a more scrupulous treatment of the initially obtained residue using column chromatography on very fine silica, which took about 80 h, tarry substances were separated and the yield of the product was increased to 37%. Unexpectedly, the isolated product turned out to be another compound, namely, *N*-(2,3-dihydroxy-4-iodo-2,3-dimethylbutyl)trifluoroacetamide **4**§ (see Scheme 3).

Molecule **4**, as distinct from **3**, has no symmetry and has two asymmetric carbon atoms. Therefore, the NCH_2 and CH_2I group protons are diastereotopic and appear in the spectrum as complex multiplets in a narrow range 3.47–3.69 ppm, which were assigned using 2D {^{1}H–^{1}H, ^{1}H–^{13}C, ^{1}H–^{15}N} NMR experiments. The presence of two chiral centers in the molecule and of only one set of signals in the ^{1}H and ^{13}C NMR spectra suggests the formation of only one (2*RS*,3*RS*)-diastereomer as racemate. The X-ray analysis showed the presence of two (2*R*,3*S*)-**4** and two (2*S*,3*R*)-**4** molecules in the unit cell (Figure 2).‡ We failed to find structural analogues of compound **4** in the literature. As by-products in the above cited $CuBr_2$-catalyzed oxidative sulfamidation of 1,3-butadienes,[1] only the products of 1,2-bromosulfamidation were formed.

Although low yields of compounds **3** and **4** do not allow one to recommend the above reaction as a preparative method, their stereoselective formation allows us to propose a tentative mechanism explaining the observed stereoselectivity of the reaction,

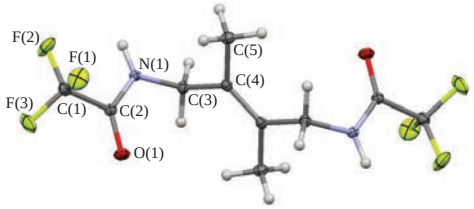


Figure 1 ORTEP diagram of *N*,*N*′-[(2*E*)-2,3-dimethylbut-2-ene-1,4-diyl]-bis(trifluoroacetamide) **3** as determined by X-ray analysis.

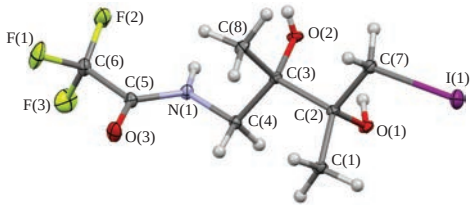


Figure 2 ORTEP diagram of *N*-(2,3-dihydroxy-4-iodo-2,3-dimethylbutyl)-trifluoroacetamide **4**; only one enantiomer is shown for clarity.

standard procedures. Commercial trifluoroacetamide and 2,3-dimethylbuta-1,3-diene (Alfa Aesar) of reagent grade were used. The reactions were followed by TLC on 60 F-254 plates, eluent hexane–diethyl ether (1:1), or hexane–diethyl ether–acetone (2:3:1). The products were separated by column chromatography on coarse (Alfa Aesar 0.060–0.200 mm) or fine (Fluka 0.015–0.035 mm) silica gel.

N,N′-*[(2E)-2,3-Dimethylbut-2-ene-1,4-diyl]bis(trifluoroacetamide)* **3**. Acetonitrile (80 ml) was added to trifluoroacetamide **1** (2 g, 18 mmol) and sodium iodide (7.95 g, 53 mmol). Then, 2,3-dimethylbuta-1,3-diene **2** (2 ml, 18 mmol) was added, the mixture was cooled to –10 °C and Bu^{t}OCl (6.1 ml, 53 mmol) was added dropwise. The reaction was carried out for 24 h in argon atmosphere in the dark. After its completion, the solvent was removed at a reduced pressure, the residue was dissolved in diethyl ether (80 ml), treated with aqueous $Na_2S_2O_3$ (80 ml) and the extract was dried over $CaCl_2$. The solvent was removed *in vacuo*, the dark-brown residue (~2.5 g) was purified on a column with coarse silica by successive elution with hexane, hexane–diethyl ether (1:1), Et_2O to afford recovered amide **1** (0.425 g, 21%) and product **3** (0.25 g, 10%). The latter was crystallized from chloroform, white crystals, mp 152 °C. IR (ν/cm^{-1}): 3323, 3094, 1703, 1557, 1344, 1279, 1211, 1180, 975, 827, 687, 623, 574, 517, 423. ^{1}H NMR (CD_3CN) δ: 1.74 (s, 3H, Me), 3.91 (d, 2H, CH_2, J 5.6 Hz), 7.58 (br.s, 1H, NH). ^{13}C NMR (CD_3CN) δ: 16.7 (Me), 43.0 (CH_2), 117.2 (q, CF_3, J 286.7 Hz), 129.5 (C), 157.9 (q, C=O, J 36.8 Hz). ^{19}F NMR (CD_3CN) δ: –76.18. Found (%): C, 41.10; H, 4.45; N, 10.15. Calc. for $C_{10}H_{12}F_6N_2O_2$ (%): C, 39.22; H, 3.95; N, 9.15.

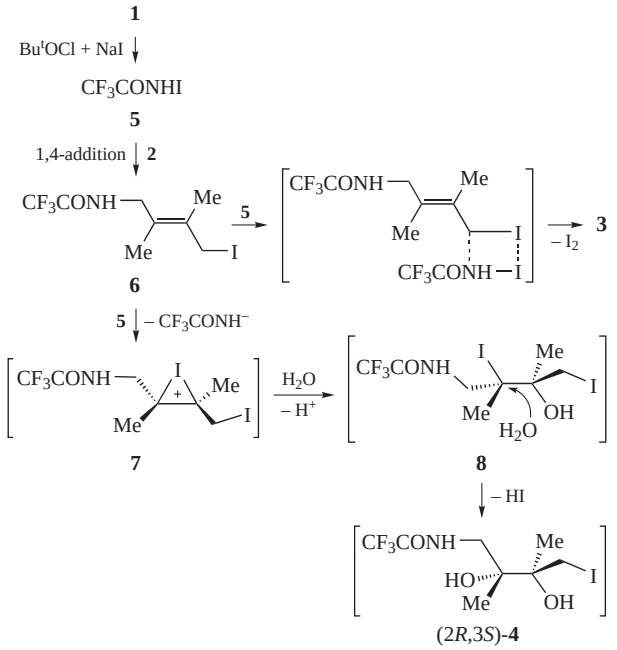
‡ *Crystal data for* **3**: $C_5H_6F_3NO$, M = 153.11, colorless needle (0.06 × × 0.10 × 0.50 mm), triclinic, space group $P\bar{1}$, at 100 K: a = 5.0888(4), b = 7.6270(6) and c = 9.1110(7) Å, α = 112.328(3)°, β = 95.026(3)°, γ = 103.060(3)°, V = 312.69(4) Å^3, Z = 2, d_{calc} = 1.626 g cm^{-3}. Total of 14733 reflections were collected (2.46° < θ < 30.12°), μ = 0.171 mm^{-1} and 1835 independent reflections (R_{int} = 0.0367), 1616 with $I > 2\sigma(I)$. The final refinement parameters were: R_1 = 0.0367, wR_2 = 0.0906 for reflections with $I > 2\sigma(I)$; R_1 = 0.0431, wR_2 = 0.0947 for all reflections; largest diff. peak/hole 0.486/–0.373 eÅ^{-3}. GOF = 1.070.

Crystal data for **4**. $C_8H_{13}F_3INO_3$, M = 355.09, colorless prism (0.31 × × 0.41 × 0.50 mm), monoclinic, space group $P2_1/c$, at 100 K: a = 13.4477(5), b = 9.5469(4) and c = 10.2342(4) Å, β = 108.6020(10)°, V = 1245.26(9) Å^3, Z = 4, d_{calc} = 1.894 g cm^{-3}. Total of 28448 reflections were collected (2.61 < θ < 30.16°), μ = 2.602 mm^{-1} and 3668 independent reflections (R_{int} = 0.0569), 2478 with $I > 2\sigma(I)$. The final refinement parameters were: R_1 = 0.0569, wR_2 = 0.1344 for reflections with $I > 2\sigma(I)$; R_1 = = 0.0883, wR_2 = 0.1521 for all reflections; largest diff. peak/hole 1.703/ –1.882 eÅ^{-3}. GOF = 1.026.

Crystal data were collected on a Bruker D8 Venture diffractometer with MoKα radiation (λ = 0.71073) using the φ and ω scans. Data were corrected for absorption effects using the multi-scan method (SADABS). The structures were solved and refined by direct methods using the SHELX programs set.[19] Nonhydrogen atoms were refined anisotropically.

CCDC 1483559 and 1483560 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ N-*(2,3-Dihydroxy-4-iodo-2,3-dimethylbutyl)trifluoroacetamide* **4**. The synthesis was carried out as above, but the residue after initial separation on a column with coarse silica (~3.1 g) was further purified on a column with fine silica (very slowly, 80 h) using the same eluting system. As a result, amide **1** (0.3 g, 15%) was recovered and product **4** (2.0 g, 37%) was crystallized from chloroform. White crystals, mp 122 °C. IR (ν/cm^{-1}): 3377, 3282, 3108, 2986, 1729, 1704, 1566, 1441, 1389, 1214, 1194, 1149, 1087, 1037, 954, 834, 746, 727, 700, 566, 525, 444. ^{1}H NMR (CD_3CN) δ: 1.16 (d, 3H, 2-Me, J 0.5 Hz), 1.27 (d, 3H, 3-Me, J 0.5 Hz), 3.22 (br.s, 1H, OH), 3.26 (br.s, 1H, OH), 3.47 (ddq, 1H, 2-CH_A, J 13.9, 4.9, 0.5 Hz), 3.52 (d, 1H, 4-CH_A, J 10.2 Hz), 3.53 (dd, 1H, 2-CH_B, J 13.9, 7.2 Hz), 3.69 (dq, 1H, 4-CH_B, J 10.5, 1.1 Hz), 7.65 (br.s, 1H, NH). ^{13}C NMR (CD_3CN) δ: 20.53 (CH_2I), 21.21 (2-Me), 23.77 (3-Me), 46.99 (NCH_2), 75.10 (2-C), 75.63 (3-C), 117.16 (q, CF_3, J 286.1 Hz), 157.96 (q, C=O, J 36.5 Hz). ^{15}N NMR (CD_3CN) δ: –273.4. ^{19}F NMR (CD_3CN) δ: –76.30. Found (%): C, 27.49; H, 3.83; N, 4.10; F, 17.15; I, 37.77. Calc. for $C_8H_{13}F_3INO_3$ (%): C, 27.06; H, 3.69; N, 3.94; F, 16.05; I, 35.74.



Scheme 4

which can be useful for choosing the conditions for oxidative amidation (Scheme 4). We suppose that the reaction starts with the formation of *N*-iodoamide **5** which reacts with diene **2** to give 1,4-adduct **6**. The latter can react with another molecule of **5** by the halophilic mechanism *via* the four-membered transition state with elimination of elemental iodine to furnish product **3**. Formation of substantial amounts of iodine is indeed observed in the course of the reaction. Alternatively, the double bond of intermediate **6** can be attacked by **5** to give the iodonium ion **7** which undergoes the ring opening by the bottom-side attack of water to afford intermediate **8** with the (2*S*,3*R*)-configuration of the chiral centers. Finally, the S_N2 hydrolysis with inversion of configuration at C-2 atom gives product **4** with the (2*S*,3*R*)-configuration. The up-side attack of compound **5** to substrate **6** will lead *via* the same sequence of transformations to product **4** with the (2*R*,3*S*)-configuration. The experimentally observed formation of racemic (2*RS*,3*RS*)-**4** product makes the proposed mechanism plausible. The formation of compound **4** in the course of long-lasting purification on silica column is reasonably consistent with the possibility of the hydrolysis with water adsorbed on silica gel.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.026.

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