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Oxidative addition/cycloaddition of arenesulfonamides and triflamide to N-allyltriflamide and N,N-diallyltriflamide†

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N-Allyltriflamide adds triflamide in the oxidative system (t-BuOCl + NaI) to give N,N,N′-propene-1,2,3-triytris(triflamide), while under the same conditions arenesulfonamides as well as trifluoroacetamide diastereoselectively give the product of chlorination/dimerization. (2R,5S)-2,5-bis(chloromethyl)-1,4-bis[(trifluoromethyl)sulfonyl]piperazine. N,N-Diallyltriflamide reacted with triflamide affords the products of iodotriflamidation of one or two C=C bonds, and the product of intramolecular iodotriflamidation, 3,7-diodo-1,5-bis[(trifluoromethyl)sulfonyl]-1,5-diazocane, and 3,7,9-tris[(trifluoromethyl)sulfonyl]-3,7,9-triazabicyclo[3.3.1]nonane. In contrast, with arenesulfonamides and trifluoroacetamide, N,N-diallyltriflamide gives the products of iodoamination or/and iodochlorination at only one double bond.

Introduction

The chemistry of triflamide (CF3SO2NH2 or TfNH2) and its derivatives has attracted the attention of chemists due to its high acidity, catalytic activity and specific chemical properties which are different from those of other sulfonamides, as was clearly demonstrated in our review. Of special interest are unsaturated derivatives of triflamide, because the presence of a multiple bond affected by a very strong electron-acceptor triflyl group increases the synthetic potential of these compounds. Until recently, very scarce information was available not only on unsaturated triflamide compounds but also for other sulfonamides as well. The first representative of N-allyltriflamides was synthesized by us in 2012. Since then, numerous unsaturated triflamide compounds having one or two double or/and triple bonds have been synthesized and investigated in different reactions.

Another fascinating field of the triflamide chemistry is the reactions of oxidative triflamidation of alkenes and dienes, leading in many cases to the products different from those obtained with arenesulfonamides. A similar specific reactivity was observed in the reactions of oxidative trifluoroacetamidation in comparison with the reactions of non-fluorinated amides. However, depending on the substrate and the oxidant, triflamide may show the same pattern of reactivity as arenesulfonamides, like it was demonstrated very recently on the example of chloroamination of a large series of indoles with triflamides and arenesulfonamides with NaClO as an oxidant. In all cases, the products of substitution (via addition–elimination), 3-chloro-2-amidoindoles, were obtained in moderate to excellent yields.

It was reasonable to assume that the study of the reactions combining these two types of transformations, that is, the reactions of oxidative triflamidation of unsaturated triflamide derivatives, would lead to new unusual structures and specific patterns of reactivity. With this in mind, in the present study we have studied the reactions of N-allyltriflamide T NhC2H2CH=C=CH2 1 with triflamide 2 and, for comparison, with arenesulfonamides 4-RC6H4SO2NH2 (R = Me, H, Cl, NO2) 3a–d and trifluoroacetamide 4 under oxidative conditions in the system (t-BuOCl + NaI). The reaction of N,N-diallyltriflamide T NhC2H2CH=C=CH2 5 with triflamide has also been studied to investigate the effect of the substrate on the course of the reaction. The reaction of N-allyltriflamide with triflamide at −30 °C proceeds in quantitative yield and affords a single product identified as N,N,N′-propene-1,2,3-triytris(triflamide) 6 (Fig. 1). The structure of product 6 was proved by 1H, 13C, 19F NMR and IR spectroscopy and elemental analysis (Scheme 1).

For comparison, we performed under the same conditions the reaction of N-allyltriflamide 1 with arenesulfonamides 3a–d (R = Me, H, Cl, NO2) and with trifluoroacetamide CF3CONH2 4. To our surprise, for the reaction both with 3 and with 4 the only product isolated in good yield was pipera zine 7. That means, that both arenesulfonamides and trifluoroacetamide act only as chlorine carriers, irrespective of their NH-acidity, which is much lower than that of triflamide (pKa vary from 11.70 for 3a to 9.48 for 3d and are equal to and 6.39 for TfNH2 and >14 for 4).
However, the yield tends to increase with the decrease of pKₐ of the amide (Table 1).

The structure of product 7 was deduced from its IR, mass, ¹H and ¹³C NMR spectra, in particular, from the absence of NH signals in ¹H NMR as well as ν NH band in IR spectrum, the presence of two pairs of diastereotopic methylene protons in the range 3.6–4.1 ppm, with respect to one unresolved multiplet of methine proton at 4.25 ppm, and the corresponding ¹³C signals at 40, 42 and 55 ppm as well as one CF₃ quartet at 120 ppm. The mass spectrum showed a low-intense peak of molecular ion m/z 446 and most intense ions with m/z 397 [M – CH₂Cl], 263 [M – CF₃SO₂ – HCl], all with proper isotope distribution. Finally, the molecular structure was determined by single crystal X-ray analysis as (2R,5S)-2,5-bis(chloromethyl)-1,4-bis[(trifluoromethyl)sulfonyl]piperazine 7.¹ Molecule 7 has S₂ mirror-rotation axis (or inversion centre Ci) passing through the center of the ring and parallel to the S–CF₃ and C–CH₂Cl bonds.

It is worth noting that N-allylamides with other electron-withdrawing groups such as Ts, PhCO or PhCS, show essentially different behavior: in the same oxidative system they undergo intramolecular cycloaromatization with the formation of 2-iodomethyl-N-tosylaziridine, 5-iodomethyl-2-phenylisoxazole or -thiazole, respectively.¹⁰ This means that, as in many other cases, unsaturated triflamide 1 exhibit specific reactivity which is distinct from that of other sulfonamides in similar reactions. The reasons for that were outlined by us earlier.²

Under the same conditions, N,N-diallyltriflamide 5 gives a whole bunch of linear and cyclic products in a moderate total yield and in comparable amounts depending on the reaction conditions (Scheme 3). With equimolar ratio of the reagents at −10 °C, the reaction mixture contains monoadduct 8, 3,7-diiodo-1,5-bis(trifluoromethylsulfonyl)-1,5-diazocane 10 and 3,7,9-tris(trifluoromethylsulfonyl)-3,7,9-triazabicyclo[3.3.1]nonane 11, along with a small amount of unreacted substrate 5. Increasing the ratio of 5 to 2 to 1 : 2 and carrying out the reaction at −30 °C results in full conversion of the reagents and formation of diadduct 9, apart from products 8, 10, 11. All reaction products were isolated as individual compounds by column chromatography and their structure was determined by ¹H, ¹³C, ¹⁹F NMR spectroscopy and, for compounds 10 and 11, also by single crystal X-ray analysis, Fig. 2 and 3, respectively. Molecule 10 has C₃ symmetry axis, and molecule 11 has the plane of symmetry passing through the sulfur and nitrogen atoms.

As with N-allyltriflamide 1, we performed the reaction of N,N-diallyltriflamide 5 with arenesulfonamides 3a-d and with trifluoroacetamide CF₃CONH₂ 4. The reaction occurred only at...
one double bond leading to the products of iodoamination 12 similar to 8, and their isoelectronic analogue 13 (Table 2). No addition to the second C=C bond takes place even with double excess of sulfonamide (on the example of NO2C6H4SO2NH2). The reasons for such inertness of the second double bond in 5 with respect to addition of sulfonamides are not clear; the only assumption is that the oxidative addition to one double bond decreases the reactivity with respect to further reaction with electrophiles, which may require harsher conditions, in which the reaction mixture undergoes resinification.

One-pot assembling of 1,5-diazocane and 3,7,9-triazabicyclo[3.3.1]nonane scaffolds shown in Scheme 3 is of interest because it was shown that the presence of the 1,5-diazocane motif in oxidative polyamine metabolites is critical for inhibiting activity and suppressing cytotoxicity. The known methods of synthesis of 1,5-diazacyclooctanes suffer from costly reagents or long-term processes (up to nine days). The present work provides the first one-pot synthesis of 3,7-diodo-1,5-bis[(trifluoromethyl)sulfonyl]-1,5-diazocane capable of further functionalization at positions 3 and 7.

As to 3,7,9-triazabicyclo[3.3.1]nonane derivatives, their synthesis is based on the cyclization of compounds having the 2,4-bis(chloromethyl)piperidine moiety under the action of amines.

The mechanism of oxidative triflamidation of compound 1 is similar to that proposed earlier and includes, as the key intermediate reagent, N-iodotriflamide which adds to the double bond of substrate 1 affording intermediate adduct 15. The latter reacts with the next molecule of 14 with elimination of molecular iodine and formation of the final product 6 (Scheme 4).

Unexpected formation of substituted piperazine 7 in the reaction in Scheme 2 could be indicative of the reaction proceeding without sodium iodide being involved. However, a special experiment showed that the formation of 7 does not occur in the absence of NaI. This allowed us to suggest the following tentative mechanism, shown in Scheme 5 and including the intermediate iononium cation 16, its opening with the formation of adduct 17, and subsequent cyclodimerization to the final product 7.

Consideration of the structure of cation 17 allows to explain the X-ray structure with two axial CH2Cl substituents in the ring. Since the bond configuration around the triflamide nitrogens is planar, the adjacent chloromethyl groups adopt axial positions in the pre-formed six-membered ring after elimination of HI in order to minimize repulsions between the triflyl and chloromethyl substituents leading to the experimentally determined structure (Fig. 1).

The mechanism of formation of the bicyclic product 11 depends on the fate of diadduct 9 (Scheme 6). Route a suggests its cyclization to the intermediate \(N,N'-(1,4-bis[(trifluoromethyl)sulfonyl]piperazine-2,6-diyl)dimethanediyl)bis(triflamide) 18, which finally gives bicycle 11 by elimination of the triflamide molecule. An alternative route b is hardly possible since the two iodine atoms in the 8-membered cycle 10 are too far from each other being in the equatorial positions of the chair,chair-conformation of the 3,7-diodo-1,5-bis[(trifluoromethyl)sulfonyl]-1,5-diazocane 10 molecule. Indeed,
special experiment showed that compound 10 taken separately was not converted to bicycle 11 under the reaction conditions, via route b.

Conclusions

In summary, we have shown that unsaturated derivatives of triflamide, being involved as substrates in oxidative addition of triflamide and arenesulfonylamine in the system (t-BuOCl + NaI), give a series of new linear, cyclic and bicyclic products, whose structure depends on the reaction conditions and the nature of the reagents. With N-allyltriflamide, triflamide and arenesulfonylamines show quite different reactivity patterns: bis-triflamidation in the former case and chlorination-dimerization in the latter. The reasons why triflamide enters the reactions of oxidative addition whereas arenesulfonylamides and trifluoroacetamide act only as positive chlorine carriers are to be examined separately.

Acknowledgements

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Notes and references

6 (a) B. A. Shainyan, M. Y. Moskalik, V. V. Astakhova, I. V. Sterkhova and I. A. Ushakov, Tetrahedron, 2015, 71, 8669; (b) V. V. Astakhova, M. Y. Moskalik, I. V. Sterkhova and B. A. Shainyan, Mendeleev Commun., 2017, 27, 293.
8 Crystallographic data were collected on a Bruker D8 Venture, μ (Mo Kα) = 0.7107 mm⁻¹ at T = 100 K. All structures were solved and refined on F² by using the SHELXS-2013 program. Crystal data for 7: C₈H₁₀Cl,F,N,O₂S₂, monoclinic, space group P2₁/c [no. 14], Z = 4, a = 8.8090(4) Å, b = 12.7998(6) Å, c = 7.2200(3) Å, β = 91.795(2)°, V = 813.68(6) Å³, Dcal = 1.825 g cm⁻³, 2θmax = 60.1°; 21 282 reflections and 2381 with I > 2σ(I); 109 parameters (C, O, N, S, F, ) Cl anisotropic, H isotropic); maximum residual electron density 0.43 e Å⁻³; R₁ = 0.026, wR₂ = 0.064. Crystal data for 10: C₈H₁₀F₆I₄N₂O₄S₂, monoclinic, space group P2₁/c
(no. 14), Z = 8, a = 11.305(2) Å, b = 17.982(3) Å, c = 18.058(3) Å, β = 100.15(1)°, V = 3613.5(9) Å³, Dc = 2.316 g cm⁻³; 2θmax = 60.3°; 147 899 reflections and 10 609 with I > 2σ(I); 434 parameters (C, O, N, S, F, I anisotropic, H isotropic); maximum residual electron density 2.09 e Å⁻³; R₁ = 0.043, wR₂ = 0.089. Crystal data for 11: C₉H₁₀F₉N₃O₆S₃, triclinic, space group P1̅ (no. 2), Z = 4, a = 11.214(4) Å, b = 11.857(5) Å, c = 14.834(7) Å, α = 73.27(1)°, β = 78.95(1)°, γ = 80.98(1)°, V = 1848.0(1) Å³, Dc = 1.883 g cm⁻³; 2θmax = 60.2°; 40 457 reflections and 9983 with I > 2σ(I); 541 parameters (C, O, N, S, F anisotropic, H isotropic); maximum residual electron density 1.48 e Å⁻³; R₁ = 0.079, wR₂ = 0.22.

9 Selected bond distances (Å) for 7: C(2)–C(3) 1.527(2), C(3)–C(4) 1.528(2), C(2)–N(1) 1.480(1), C(3)–N(1) 1.482(1), C(4)–Cl(1) 1.785(1), C(1)–S(1) 1.8362(14), S(1)–O(1) 1.423(1), S(1)–N(1) 1.606(1), C(1)–F(1) 1.325(2).


11 Selected bond distances (Å) for 10: C(3)–C(4) 1.520(6), C(2)–C(4) 1.515(5), C(2)–N(2) 1.483(2), C(3)–N(1) 1.490(2), C(6)–C(7) 1.519(4), C(7)–C(8) 1.515(5), C(6)–N(1) 1.482(3), C(8)–N(2) 1.490(3), C(4)–I(1) 2.159(3), C(7)–I(2) 2.165(3). The I···I interatomic distance is 7.7 Å.

12 Selected bond distances (Å) for 11: C(2)–C(3) 1.533(5), C(3)–C(4) 1.535(3), C(2)–N(1) 1.476(2), C(3)–N(3) 1.479(2), C(7)–C(8) 1.522(4), C(7)–C(9) 1.533(6), C(9)–N(1) 1.467(2), C(8)–N(2) 1.465(3), C(4)–N(2) 1.480(3), C(7)–N(3) 1.485(3).


