Oxidative addition/cycloaddition of arenesulfonamides and triflame to N-allyltriflame and N,N-diallyltriflame†

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N-Allyltriflame adds triflame in the oxidative system (t-BuOCl + NaI) to give N,N′,N″-propane-1,2,3-triyltris(triflame), 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′-Diallyltriflame reacted with triflame affords the products of iodotriflameation of one or two C=C bonds, and the product of intramolecular iodotriflameation, 3,7-diodo-1,5-bis[(trifluoromethyl)sulfonyl]-1-diazocene, and 3,7,9-tris[(trifluoromethyl)sulfonyl]-3,7,9-triazabicyclo[3.3.1]nonane. In contrast, with arenesulfonamides and trifluoroacetamide, N,N-diallyltriflame gives the products of iodoamidation or/and iodochlorination at only one double bond.

Introduction

The chemistry of triflame (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 triflame, because the presence of a multiple bond affected by a very strong electron acceptor trifl group increases the synthetic potential of these compounds. Until recently, very scarce information was available not only on unsaturated triflame compounds but also for other sulfonamides as well. The first representative of N-alkenyltriflamides was synthesized by us in 2012. Since then, numerous unsaturated triflame compounds having one or two double or/and triple bonds have been synthesized and investigated in different reactions.

Another fascinating field of the triflame chemistry is the reactions of oxidative triflameation 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 nonfluorinated amides. However, depending on the substrate and the oxidant, triflame may show the same pattern of reactivity as arenesulfonamides, like it was demonstrated very recently on the example of chloroamidation 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-amiindoindoles, 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 triflameation of unsaturated triflame 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-allyltriflame TfNCH₂CH═CH₂ 1 with triflame 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′-diallyltriflame TfN(=CH₂CH═CH₂) 5 with triflame has also been studied to investigate the effect of the substrate on the course of the reaction.

The reaction of N-allyltriflame with triflame at −30 °C proceeds in quantitative yield and affords a single product identified as N,N′,N″-propane-1,2,3-triyltris(triflame) 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-allyltriflame 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 piperazine 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 triflame (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 with m/z 446 and most intense ions with m/z 397 [M – CH₂Cl] and 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. Molecule 7 has S₂ mirror-rotation axis (or inversion centre Cₛ) 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 like Ts, PhCO or PhCS, show essentially different behaviour: in the same oxidative system they undergo intramolecular cyclization with the formation of 2-iodomethyl-N-tosylaziridine, 5-iodomethyl-2-phenylisoxazole or -thiazole, respectively. This means that, as in many other cases, unsaturated triflamine 1 exhibit specific reactivity which is distinct from that of other sulfonamides in similar reactions. The reasons for that were outlined by us earlier.

Under the same conditions, N,N-diallyltriflamine 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-diodo-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-allyltriflamine 1, we performed the reaction of N,N-diallyltriflamine 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-diaza[3,3,1]cyclooctanes suffer from costly reagents or long-term processes (up to nine days). The present work provides the ﬁrst one-pot synthesis of 3,7-diido-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 trilamidation of compound 1 is similar to that proposed earlier and includes, as the key intermediate reagent, N-iodotrimellitamide 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 iodonium cation, its opening with the formation of adduct 17, and subsequent cyclo- dimerization 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 trilamidated nitrogen atoms is planar, the adjacent chloromethyl groups adopt axial positions in the pre-formed six-membered member ring after elimination of HI in order to minimize repulsions between the trityl 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(trilamidamide) which ﬁnally gives bicycle 11 by elimination of the trilamidated 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-diiodo-1,5-bis[(trifluoromethyl)sulfonyl]-1,5-diazocane 10 molecule.
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 triflimide, being involved as substrates in oxidative reactions with triflimide and arenesulfonamides 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-allyl triflimide, triflimide and arenesulfonamides show quite different reaction patterns: bis-triflimidation in the former case and chlorination–dimerization in the latter. The reasons why triflimide enters the reactions of oxidative addition whereas arenesulfonamides and trifluoroacetamide act only as positive chlorine carriers are to be examined separately.

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Notes and references

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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 F by using the SHELXS-2013 program. Crystal data for 7: C₁₆H₁₄ClF₃N₃O₂S₂, monoclinic, space group P2₁/c (no. 14), Z = 4, a = 8.8900(4) Å, b = 12.7998(6) Å, c = 7.2200(3) Å, β = 91.795(2)°, V = 183.68(6) Å³, Dc = 1.825 g cm⁻³, 2θ max = 60.1°; 21 282 reflections and 2381 with I > 2σ(I); 109 parameters (C, O, N, S, F, I, Cl anisotropic, H isotropic); maximum residual electron density 0.43 e Å⁻³; R₁ = 0.026, wR₂ = 0.064. Crystal data for 10: C₁₆H₁₆F₃N₃O₂S₂, monoclinic, space group P2₁/c.
(no. 14), Z = 8, a = 11.305(2) Å, b = 17.982(3) Å, c = 18.058(3) Å, \( \beta = 100.15(1) \), \( V = 3613.5(9) \) Å³, \( D_c = 2.316 \) g cm⁻³; 147 899 reflections and 10 609 with \( I > 2\sigma(I) \); 434 parameters (C, O, N, S, F, I anisotropic, H isotropic); maximum residual electron density 2.09 e Å⁻³; \( R_1 = 0.043, wR_2 = 0.089 \).

Crystal data for 11: \( C_9H_{10}F_9N_3O_6S_3 \), triclinic, space group \( P\bar{1} \) (no. 2), Z = 4, a = 11.214(4) Å, b = 11.857(5) Å, c = 14.834(7) Å, \( \alpha = 73.27(1) \), \( \beta = 78.95(1) \), \( \gamma = 80.98(1) \), \( V = 1848.0(1) \) Å³, \( D_c = 1.883 \) g cm⁻³; \( \theta_{\text{max}} = 60.2 \); 40 457 reflections and 9983 with \( I > 2\sigma(I) \); 541 parameters (C, O, N, S, F anisotropic, H isotropic); maximum residual electron density 1.48 e Å⁻³; \( R_1 = 0.079, wR_2 = 0.22 \).

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).

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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).

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