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Unusual [2+2]-cycloaddition of carbodiimides to *N*-alkenylidenetriflamides

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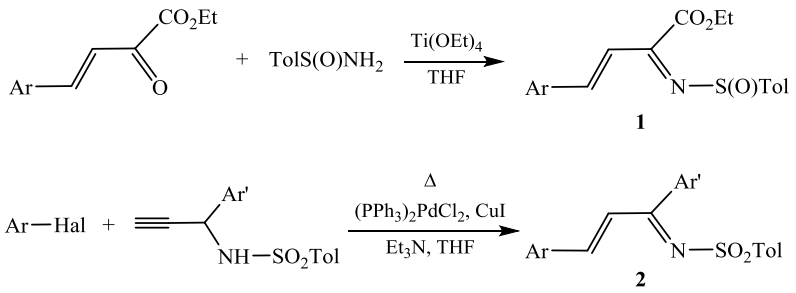
A B S T R A C T

An unusual [2+2]-cycloaddition to the C=C bond of 1-azadienes has been observed for the first time using the example reaction of 1,3-*N*-trifluoromethylsulfonyl-1-azabutadienes with carbodiimides. The structure of *N*-{[2,2-dimethyl-1-cyclohexyl-4-(cyclohexylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamide, formed from dicyclohexylcarbodiimide and *N*-(3-methylbut-2-en-1-ylidene)trifluoromethanesulfonamide, was proved by single crystal X-ray analysis.

Keywords:
N-[1-Alkyl-4-(alkylimino)-3-azetanyliden]methyl(trifluoro)methanesulfonamides
2,2-Dipolar cycloaddition reaction
1,3-*N*-Trifluoromethylsulfonyl-1-azabutadienes
Single crystal X-ray

1-Azadienes are reactive species which can act as heterodienes in the Diels-Alder reaction with various dienophiles providing a straightforward and atom economical route to nitrogen-containing heterocycles possessing diverse biological activities.[1–4] The simplest method for the synthesis of 1-azadienes is the condensation of α,β-unsaturated carbonyl compounds with amines. Of special interest are electron-deficient 1-azadienes, for which in a recent review[4] two methods were described. The first method uses the condensation of toluenesulfinimide ($TolS(O)NH_2$) with β,γ-unsaturated α-ketoesters ($ArCH=CHC(O)CO_2Et$) to give ethyl 5-aryl-3-[(tolylsulfinyl)imino]pent-4-enoates ($ArCH=CHC(CO_2Et)=NS(O)Tol$),[5] while the second uses the Sonogashira reaction of aryl halides (ArX) with *N*-(1-arylprop-2-yn-1-yl)tosylamides ($TsNHCH(Ar')C\equiv CH$) followed by isomerization to give *N*-[1-aryl-3-arylprop-2-en-1-ylidene]-tosylamides ($TsN=C(Ar')CH=CHAr$)[6] (Scheme 1).



Scheme 1. Synthesis of electron-deficient 1-azadienes.

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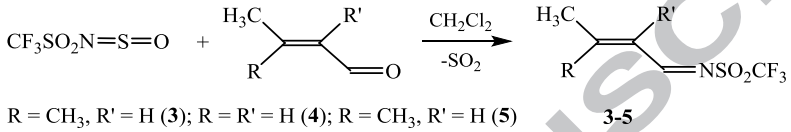
In the above examples, the electron withdrawing group is either the TolSO (in **1**) or $TolSO_2$ group (in **2**). The interest in electron-deficient 1-azadienes is connected with their ability to react as electrophiles in 1,4-additions and to enter the reactions with electron-rich dienophiles in the inverse electron-demand hetero Diels-Alder reactions.[3,5,7,8]

Recently, we have reported the synthesis of alkenylidenetriflamides (TfN=CH–CR=CR'CH_3) *via* the reaction of *N*-sulfinyltriflamide (TfNSO) with the corresponding α,β-unsaturated aldehydes,[9] which provided the opportunity to investigate these new electron-deficient 1-azadienes in cycloaddition reactions (Scheme 2).



R = CH_3, R' = H (**3**); R = R' = H (**4**); R = CH_3, R' = H (**5**) **3-5**

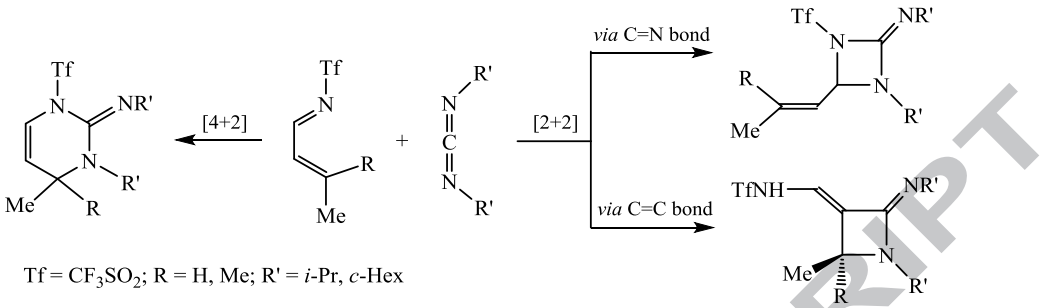
Scheme 2. Synthesis of 1-trifluoromethylsulfonyl-1-azadienes.

Electron-deficient 1-azadienes are known to react with different dienophiles, such as ketene acetals,[1] enamines,[8] vinyl ethers,[1,10] vinyl esters,[2] alkenes,[2] methyl vinyl ketones,[11] sulfenes ($CH_2=SO_2$),[12] ketenes,[13] and enolizable ketones[14] or undergo dimerization[8] *via* a [4+2]-cycloaddition mechanism. The regioselectivity of cycloaddition is determined by the polarization of the dienophile C=C bond.

Much less common is the [2+2]-cycloaddition reaction of 1-azadienes. As summarized in a review by Mahajan and co-workers,[2] 1-azadienes usually form four-membered cycloadducts with ketenes as the second addends, and it was specially noted that 'only the C=N double bond of the azadienes is involved in these [2+2]-cycloadditions'.[2] It is also worth noting that alkenes enter the [2+2]-cycloaddition reaction with keteneiminium triflates ($[RR'C=C=N(CH_2CH=CH_2)_2]^+ TfO^-$) only with participation of the C=C bond of the latter.[15]

Taking into account the unique behavior of the triflamide derivatives,[16] which often demonstrate patterns of reactivity different from those of arenesulfonamides and to which our new *N*-triflyl 1-azadienes obviously belong, we tried the reaction of 1-azadienes (TfN=CH–CH=C(R)Me, R = Me (**3**), H (**4**)) with carbodiimides (R'N=C=NR', R' = *c*-C_6H_{11} (**6**), *i*-C_3H_7 (**7**)). Carbodiimides as addends were used, taking into account their ability to enter into cycloaddition reactions; in particular, we have found that *N*-sulfinyltriflamide (TfNSO) gives *N*-triflyl-1,2,4-thiadiazetidin-3-imine 1-oxides *via* a [2+2]-cycloaddition/ring opening/ring closure sequence of transformations.[17] As far as we are aware, there are no reports of the reactions of 1-azadienes with carbodiimides.

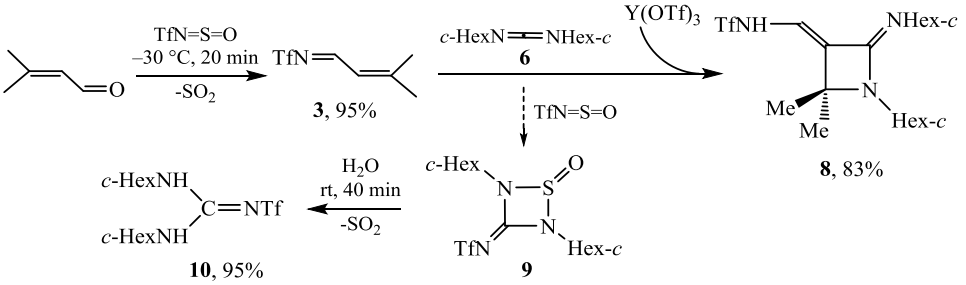
The reaction of 1-azadienes **3**, **4** with carbodiimides **6**, **7** may proceed either as a [4+2] or [2+2]-cycloaddition, and in the latter case, either with the C=C or C=N bond.



Scheme 3. Possible pathways for the cycloaddition of carbodiimides to alkenylidenetriflamides.

Since *N*-triflyl-1-azadienes (TfN=CH–CR=CR'R") were shown to be hydrolytically unstable, decomposing to the starting enals and triflamide,[9] for the reaction with carbodiimide **6** we used the *in situ* formed 1-azadiene **3**, without its isolation from the reaction mixture. For this, a solution of *N*-sulfinyltriflamide in CH_2Cl_2 was added to a solution of 3-methyl-2-butenal in the same solvent under an inert atmosphere at –40 to –30 °C, stirred for 1 h and allowed to stand overnight at 4 °C to complete the first reaction step (Scheme 4). Then, to the obtained solution of 1-azadiene **3**, carbodiimide **6** was added at a temperature not exceeding –20 °C, stirred for 30 min and left to stand overnight in a refrigerator at –18 °C. After 16 h, the crystalline product **8** was precipitated.[18]

It is important to note that the two steps in Scheme 4 must be performed separately, otherwise TfNSO can react with carbodiimide **6** resulting in formation of *N*-trifluoromethanesulfonyl-2,4-dicyclohexyl-1,2,4-thiadiazetidin-3-imine 1-oxide **9**,[17] which is what occurred when the enal, TfNSO and carbodiimide were mixed simultaneously or when excess TfNSO was present in the reaction mixture. The 1,2,4-thiadiazetidin-3-imine 1-oxide **9** was further hydrolyzed to give *N*-triflylguanidine **10**. This route was proved by isolation of a crystalline product from the reaction with simultaneous mixing of the reagents; its single crystal X-ray structure coincided with that earlier obtained for compound **10** by our research group.[19]



Scheme 4. Reaction of the *in situ* formed 1-azadiene **3** with dicyclohexylcarbodiimide **6** catalyzed by $Y(OTf)_3$.

The structure of heterocyclization product **8** was confirmed by spectroscopic methods[20] and proved by single crystal X-ray analysis (Fig. 1).[21]

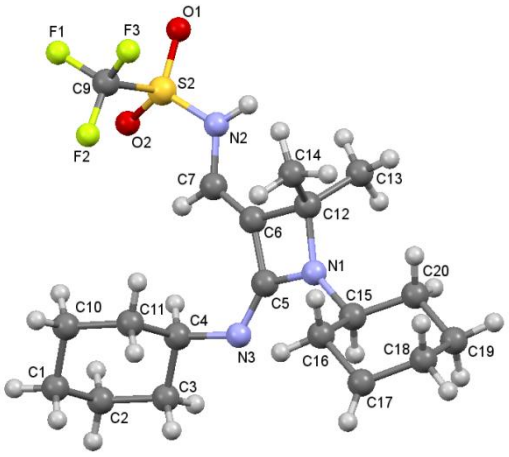
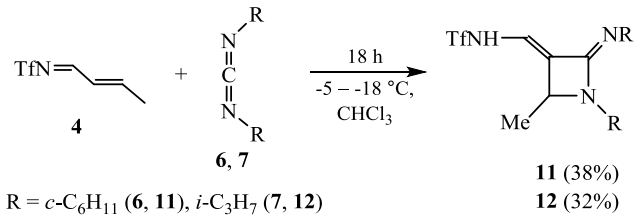


Figure 1. Single crystal X-ray structure of *N*-{[2,2-dimethyl-1-cyclohexyl-4-(cyclohexylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamide **8**.

Taking into account the moderate yield (~35%) and the fact that heterocyclization reactions of 1-azadienes are often catalyzed by Lewis acids,[3,8,10] in particular, metal triflates, we performed the reaction of the *in situ* formed azadiene **3** in the presence of 1 mol% $Yb(OTf)_3$, which was added to the reaction mixture before the addition of carbodiimide **6**. Notably, the use of $Yb(OTf)_3$ may change the course of the reaction, directing it to the dimerization of the 1-azadiene and the formation of tetrahydropyridines.[8] In our case, however, the use of $Yb(OTf)_3$ substantially increased the yield, to 83%, and no dimer was formed.

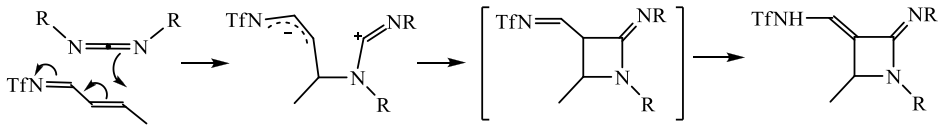
The more stable 1-azadiene **4** directly reacted with either carbodiimides **6** or **7** at –5 °C, stirred at this temperature for 20 min and left to stand overnight in a refrigerator (–18 °C); to give the corresponding azetidines after 18 h (Scheme 5).[17]



Scheme 5. Reaction of 1-azadiene **4** with carbodiimides **6**, **7**.

Therefore, the reaction of 1,3-*N*-trifluoromethylsulfonyl-1-azabutadienes with carbodiimides represents the first example of a [2+2]-cycloaddition reaction to the C=C bond of

1-azadienes. Although the detailed mechanism remains to be elucidated, the following tentative scheme can be proposed (Scheme 6).



Scheme 6. Tentative mechanism for the $[2_{C=C} + 2_{C=N}]$ cyclization of 1-azadienes with carbodiimides.

The proposed mechanism is supported by the observation that the IR spectra of the reaction mass before crystallization (apart from the bands of products **8**, **11**, **12** at 1689 and 1645 cm^{-1}) consists of intense bands at 1584–1594 cm^{-1}, which can be assigned to the intermediate azetidines containing the TfN=C moiety, and coincide with the band in the IR spectra of the earlier obtained *N*-triflylimines (TfN=CRR').[23]

The reason why *N*-alkenylidenetriflamides react with carbodiimides *via* their C=C double bond, while ketenes react with 1-azadienes *via* addition to the C=N double bond[2] is evident: the latter reactions include nucleophilic 1-azadienes, bearing no electron-withdrawing groups at nitrogen, so, the reaction proceeds as a nucleophilic addition of the *N*-nucleophile to the C=O group. *N*-Alkenylidenetriflamides act as electrophiles and, at first glance, the attack of carbodiimide should be directed to the most electrophilic C=N carbon. However, in this case, the incipient negative charge would be located on the triflamide nitrogen, while for attack on the terminal C_{sp2} atom, as depicted in Scheme 6, it is delocalized over the N=CH=C tryad, thus stabilizing the system.

In summary, we have found that the reaction of 1,3-*N*-trifluoromethylsulfonyl-1-azabutadienes with carbodiimides proceeds as a [2+2]-cycloaddition reaction leading to 2-substituted *N*-{[1-alkyl-4-(alkylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamides and represents the first example of addition to 1-azadienes involving the C=C rather than the C=N bond. The structure of the products was proved by IR and NMR spectroscopy as well as single crystal X-ray analysis. Taking into account the strong acceptor character of the triflyl group, a mechanism was proposed to explain the unusual course of the reaction.

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18. When stored at room temperature, the reaction mixture polymerized, did not crystallize, and the yield of **8** decreased. The same occurred for products **11**, **12**.
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20. *N*-{[2,2-Dimethyl-1-cyclohexyl-4-(cyclohexylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamide **8**; yield 83% (from the $Y(OTf)_3$-catalyzed reaction), m.p. 212 °C (white crystals, from EtOH); $IR_{\nu max}$: 3242, 2936, 2859, 1689, 1645, 1366, 1299, 1255, 1196, 1178, 1110, 953, 884, 607 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.64 (1H, br.s, NH), 7.15 (1H, s, CH=N), 3.62 (1H, m, =NCH), 3.22 (1H, m, NCH), 1.53 (6H, s, CH_3), 1.93–1.70, 1.65–1.40, 1.40–1.05 (20H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.3 (C=N), 139.8 (CH=<u>C</u>), 120.8 q (CF_3, J = 326.6 Hz), 112.8 (<u>C</u>H=C), 72.4 (=NCH), 54.2 (<u>C</u>Me_2), 53.8 (NCH), 32.5 (=NCH<u>C</u>H_2), 30.7 (NCH<u>C</u>H_2), 25.1 (NCHCH_2<u>C</u>H_2), 24.6 (CH_3), 24.5 (CH_3), 24.10 (=NCHCH_2<u>C</u>H_2), 24.06 (C^4 in cyclohexyl rings); ^{19}F NMR (376 MHz, DMSO-d_6) δ: –77.73. Anal. calcd for $C_{19}H_{30}F_3N_3O_2S$, %: C 54.14; H 7.17; N 9.97; S 7.61; found, %: C 54.11; H 7.28; N 9.46; S 7.50.

    N-{[2-Methyl-1-cyclohexyl-4-(cyclohexylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamide **11**; yield 32%, m.p. 163 °C (colorless crystals, from EtOH); $IR_{\nu max}$: 3250, 2935, 2860, 1683, 1645, 1372, 1307, 1259, 1196, 1119, 969, 888, 610 cm^{-1}. ^1H NMR (400 MHz, CD_3CN) δ: 7.37 (br.s, 1H, NH), 6.78 (s, 1H, CH=N), 4.60 (q, J = 6.0 Hz, 1H, C<u>H</u>CH_3), 3.45 (m, 1H), 3.37 (m, 1H), 2.17 (m, 2H), 1.51 (d, J = 6.0, 3H, CHC<u>H</u>$_3$), 1.81 (m, 6H), 1.65 (m, 2H), 1.35 (m, 10H); ^{13}C NMR (100 MHz, CD_3CN) δ: 160.1 (C=N), 143.4 (<u>C</u>=CH), 121.8 (q, J = 324.4, CF_3), 108.2 (C=<u>C</u>H), 62.0, 55.0, 33.5, 33.4, 32.4, 30.6, 25.7, 25.6, 25.5, 25.2, 19.0; ^{19}F NMR

(376 MHz, CD_3CN) δ: –78.67. Anal. calcd for $C_{18}H_{28}F_3N_3O_2S$, %: C 53.05; H 6.93; N 10.31; S 7.87; found, %: C 52.93; H 6.92; N 10.25; S 7.55.

N-{[1-Isopropyl-2-methyl-4-(isopropylimino)azetidin-3-ylidene]methyl}trifluoromethanesulfonamide **12**; yield 38%, m.p. 183 °C (white crystals, from EtOH); IR_{vmax}: 3263, 2978, 2935, 1682, 1645, 1373, 1257, 1197, 1181, 1117, 958, 881, 604 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 7.41 (br.s, 1H, NH), 6.84 (s, 1H, CH=N), 4.62 (q, *J* = 6.1, 1H, C*H*CH_3), 3.82 (m, 2H, C*H*Me_2), 1.51 (d, *J* = 6.1, 3H, CHC*H*$_3$), 1.24 (m, 12H, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, CD_3CN) δ: 160.5 (C=N), 143.43 (*C*=CH), 122.1 (q, *J* = 122.1, CF_3), 108.7 (C=*C*H), 61.9 (C=N*C*H), 48.3 (N*C*HCH_3), 47.8 (N*C*HMe_2), 22.9, 22.8, 21.7, 19.9, 19.0 (CH_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ: –79.00. HRMS, *m/z*: calcd for $C_{12}H_{21}F_3N_3O_2S$ [$(M+H)^+$] 328.1307, found 328.1330; Anal. calcd for $C_{12}H_{20}F_3N_3O_2S$, %: C 44.03; H 6.16; N 12.84; S 9.80; found, %: C 44.09; H 6.09; N 12.90; S 9.79.

21. Crystal data for **8**: $C_{19}H_{30}F_3N_3O_2S$, *M* 421.52, colorless plates, m.p. 212 °C, 0.500×0.400×0.030 mm^3, triclinic, space group P-1, cell parameters: *a* 9.8847(6), *b* 10.5093(7), *c* 11.5856(8) Å, α 77.624(2), β 67.468(2), γ 88.073(2), *V* 1084.25(12), *Z* 2, d_{calc} 1.291 g/cm^3. 58125 reflections collected on a Bruker D8 Venture diffractometer with MoK_α radiation (λ = 0.71073) in the range 2θ = 3.90 to 60.74°, of which 6476 are unique. 369 variables refined: R_1 = 0.0468, wR_2 = 0.1178 [I >2σ(I)] and R_1 = 0.0637, wR_2 = 0.1269 [all data].[22] CCDC 1478264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033.
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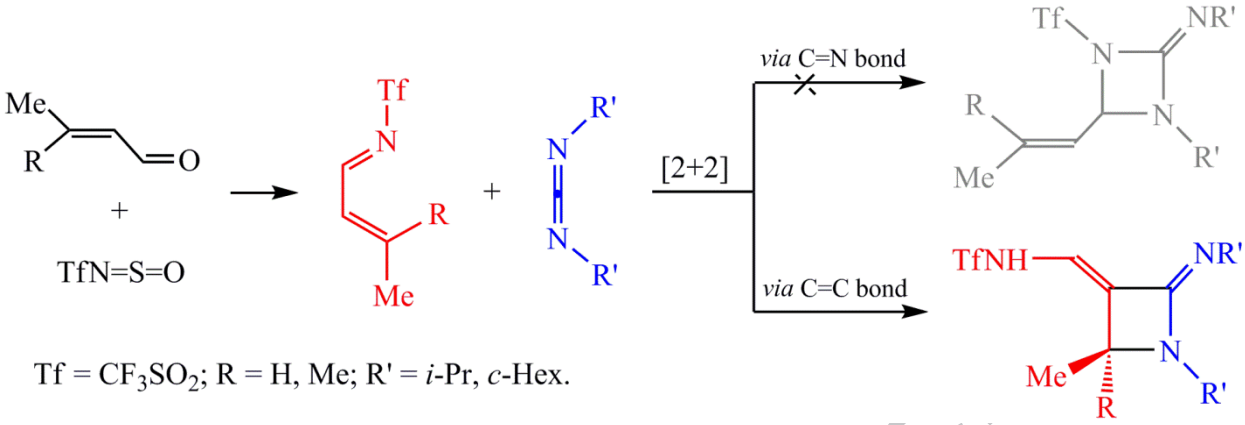
Graphical abstract



Tf = CF_3SO_2; R = H, Me; R' = *i*-Pr, *c*-Hex.

Highlights

> Unusual [2+2]-cycloaddition of carbodiimides to 1,3-*N*-trifluoromethylsulfonyl-1-azabutadienes was first observed.

> The structure of the formed *N*-{[1-alkyl-4-(alkylimino)azetidin-3-ylidene]methyl}triflamides was proved by single crystal X-ray analysis.

> The mechanism of the reaction was proposed.