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Insertion of carbon disulfide into the diaziridine ring of 6-aryl-1,5-diazabicylo[3.1.0]hexanes assisted by ionic liquids

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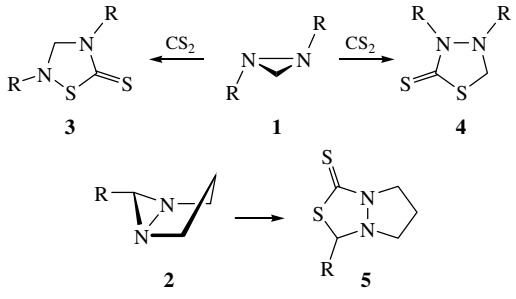
3-(4-Aryl)dihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole-1-thiones have been synthesised by the title reaction catalysed by $Et_2O{\cdot}BF_3$.

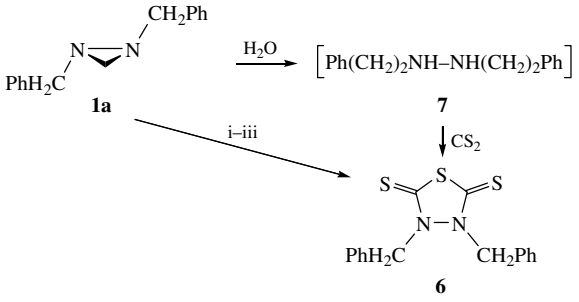
The reactions of diaziridines with electrophilic reagents occur *via* a zwitter-ionic intermediate, the transformation of which can result in the expansion of the diaziridine ring to give nitrogen-containing heterocycles with a greater number of ring atoms.[1–3] We have recently shown that the conversion of readily available 1,2-dialkyldiaziridines and their bicyclic analogues, 1,5-diazabicyclo[3.1.0]hexanes, with heterocumulenes (ketenes, isocyanates and isothiocyanates) offers new simple methods for the synthesis of 1,3-dialkylimidazolidin-4-ones, 1-mono- and 1,2-diacylpyrazolidines, 4-aroyl-1,2,4-triazolidin-3-ones and 4-benzoyl-1,2,3-trialkyl-1,2,4,6-tetrazepan-5-thiones.[4–7] Note that, depending on the heterocumulene used and the structure of the starting diaziridine derivatives, the three-membered ring in monocyclic diaziridines **1** is opened at both N–N and C–N bonds, whereas in bicyclic diaziridines **2** it is opened at the C–N bond. In this work, we continued studies on the reactions of 1,2-dialkyldiaziridines **1** and 1,5-diazabicyclo[3.1.0]hexanes **2** with electrophilic reagents using carbon disulfide. Based on the data obtained previously,[4–7] it could be expected that possible conversion products of 1,2-dialkyldiaziridines **1** include 1,2,4-thiadiazolinine-5-thione derivatives **3** or 1,3,4-thiadiazolinine-2-thione derivatives **4**, whereas the reaction of bicyclic compounds **2** with carbon disulfide most likely involves the C–N bond cleavage to give bicyclic system **5** (Scheme 1).



Scheme 1

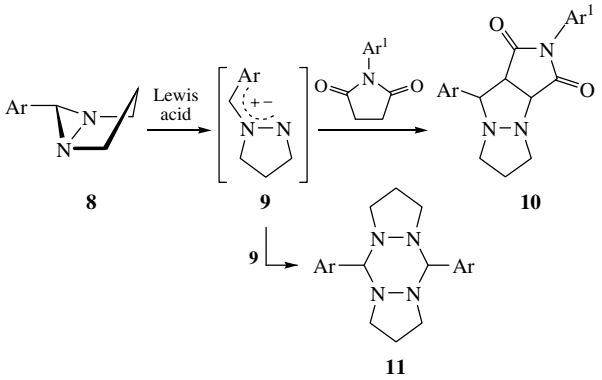
The study started with an attempt to insert CS_2 into the three-membered ring of 1,2-dialkyldiaziridines **1** using compound **1a** (R = CH_2CH_2Ph) as an example. For this purpose, a mixture of the reagents was kept for 20–72 h at 20 °C or refluxed with an excess of CS_2 in the presence of bases (TEA, NaOH). However, diaziridine **1a** did not react with CS_2 under the conditions studied and was returned unchanged from the reaction mixture. The failure of these experiments is presumably due to the rather low electrophilicity of CS_2.

Various conditions were used to intensify the reaction of diaziridine **1a** with CS_2, in particular, heating in acetonitrile in a sealed tube at 100 °C and stirring at 20 °C in the ionic liquid [bmim][BF_4] or without a solvent but in the presence of a catalytic amount of $Et_2O{\cdot}BF_3$; in all cases, the optimum molar ratio **1a**:CS_2 was 1:4. Complete conversion of diaziridine **1a** took 10 days in acetonitrile, 4 days in the ionic liquid and 25 days in the presence of $Et_2O{\cdot}BF_3$. However, in all cases, instead of expected compounds **3** or **4**, 3,4-di(2-phenylethyl)-1,3,4-thiadiazolidine-2,5-dithione **6** was obtained in 30–35% yields. 3,4-Disubstituted 1,3,4-thiadiazolidin-2,5-dithiones have been obtained by reactions of 1,2-disubstituted hydrazines with an excess of CS_2.[8] Apparently, diaziridine **1a** undergoes hydrolysis under the test conditions to give 1,2-di(2-phenylethyl)hydrazine **7**, which then reacts with CS_2 (Scheme 2). Hydrolysis to give hydrazines is a typical reaction of diaziridines.[9]



Scheme 2 *Reagents and conditions*: i, MeCN, 100 °C, 10 days; ii, [bmim][BF_4], 20 °C, 4 days; iii, without solvent, $Et_2O{\cdot}BF_3$, 20 °C, 25 days.

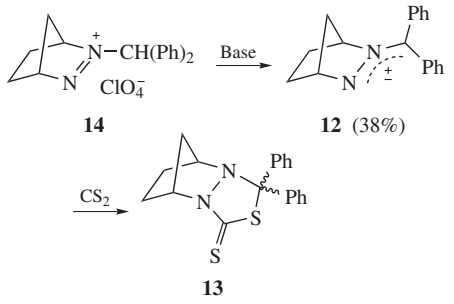
To study the insertion of CS_2 into the diaziridine ring of 1,5-diazabicyclo[3.1.0]hexane derivatives **2**, conditions found elsewhere[10,11] for a similar reaction of 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **8** with reactive dipolarophiles (*N*-arylmaleinimides) were chosen. The catalytic diaziridine ring opening in compounds **8** on treatment with Lewis acids [$Et_2O{\cdot}BF_3$ or $In(OTf)_3$] results in dipolar intermediate **9**, which undergoes 1,3-dipolar cycloaddition to *N*-arylmaleinimides to give product **10** as a mixture of *cis–trans* isomers. If no dipolarophile is present, intermediate **9** gives dimer **11** (Scheme 3). These reactions



Scheme 3

were carried out at room temperature in dipolar aprotic solvents, such as THF, diethyl ether and acetonitrile.

Furthermore, the possibility of CS_2 addition to intermediate **12**, which is structurally similar to intermediate **9**, followed by cyclization into tricyclic system **13** has been shown experimentally.[12] Compound **12** was synthesised by passing a solution of diazenium perchlorate **14** through a column with alkaline alumina (Scheme 4).



Scheme 4

The catalytic opening of 1,5-diazabicyclo[3.1.0]hexanes **2** with an excess of CS_2 in the presence of $Et_2O{\cdot}BF_3$ was first carried out for 6-(4-methoxyphenyl)-1,5-diazabicyclo[3.1.0]-hexane **8a** in acetonitrile at 20 °C. This reaction gave target 4-aryl-3-thia-1,5-diazabicyclo[3.3.0]octane-2-thione **5a**,† but the complete conversion of compound **8a** took as long as 20 days. To accelerate the process, the same reaction was carried out in the ionic liquid [bmim][BF_4] or [bmim][PF_6], which accelerate 1,3-dipolar cycloaddition reactions.[13,14] The reaction of bicyclic compound **8a** with CS_2 in ionic liquids was carried out at room temperature and the molar ratio **8a**:CS_2 of 1:6. The reaction was monitored by TLC until complete conversion of bicyclic compound **8a**. TLC monitoring of this reaction showed that the first reaction steps produce two compounds with R_f 0.40 and R_f 0.70 in hexane–ethyl acetate (2:1). The first compound predominates initially but disappears as the reaction proceeds, whereas the amount of the second compound, presumably target bicycle **5a**, increases. The ^{1}H NMR spectrum of a mixture of these products exhibited the signals of both compounds. The signals belonging to product **5a** are 2.55 (m, 2H, NCH_2CH_2), 2.75, 3.15 (2m, 2H, $ArCNCH_2$), 3.78, 3.93 (2m, 2H, $SCNCH_2$) and 5.75 (s, 1H, SCH). The signals of substituents at the aromatic ring in the ^{1}H NMR spectrum of the second compound are shifted downfield by 0.1 ppm, there is no singlet near δ 5.75, but a singlet appears at about δ 9.85–10.0 and the aromatic proton signals are shifted downfield. Obviously, the second compound with R_f 0.4 is an intermediate reaction product. The reaction was completed in 4 h to give compound **5a** in a nearly quantitative yield.

Other 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **8b–e** were also used in the reaction with CS_2 under the conditions found. The reactions were continued until the complete conversion of starting compounds **8**; TLC monitoring showed that an intermediate was formed in all cases. The reaction time and the resulting yields of bicyclic compounds **5b–e** depended on the type of substituent in the aromatic moiety of starting compounds **8** (Table 1, Scheme 5).†,‡ Nearly quantitative yields are observed with electron-donating substituents (compounds **8c**,**d**), whereas with Ar = 4-ClC_6H_4 (compound **8e**), the yield of corresponding bicyclic compound **5e** is as low as 30%; furthermore, *p*-ClC_6H_4CHO was isolated as a by-product.

Table 1 shows that for bicycles **8a–d** the longest reaction time was observed in case of compound **8d**. Therefore, the reaction of compound **8d** with CS_2 was chosen to separate intermediate and final products. The mixture of two reaction products was extracted from the ionic liquid at the initial stage of the process, and they could be separated by column chromatography on SiO_2. It was found that the intermediate, both in an individual state obtained after evaporating the solvent and in

† All the new compounds exhibited satisfactory elemental analyses. IR spectra were measured on a UR-20 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz for ^{1}H; 75.5 MHz for ^{13}C) spectrometer ($CDCl_3$ was used as an internal standard). ^{13}C NMR spectra were recorded under proton decoupling conditions. Signals in the ^{13}C NMR spectra of compounds **5** were assigned using the selective heteronuclear double resonance method, while those in the ^{1}H NMR spectra were assigned using the NOE.DIFF method for compound **5c** as an example. Mass spectra were measured on a Finnigan MAT INCOS-50 instrument. TLC was carried out on Silufol UV-254 plates. Melting points were measured on a Gallenkam.p. instrument (Sanyo).

*3-(4-Methoxyphenyl)dihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole-1-thione* **5a**: R_f 0.71 [*n*-hexane–ethyl acetate, 2:1 (v/v)], mp 131.5–132.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.55 (m, 2H, NCH_2CH_2, ^2J 9.2 Hz, ^3J 5.5 Hz), 2.75, 3.15 (2m, 2H, $ArCNCH_2$, ^2J 9.3 Hz, ^3J 5.5 Hz, $\Delta\nu$ 112.7 Hz), 3.78, 3.93 (2m, 2H, $SCNCH_2$, ^2J 9.2 Hz, ^3J 5.5 Hz, $\Delta\nu$ 46.2 Hz), 3.83 (s, 3H, OMe), 5.75 (s, 1H, SCH), 6.80, 7.50 (2d, 4H, $C_{Ar}H$, ^3J 10.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 27.66 (NC*C*), 45.82 (SCN*C*C), 51.35 (ArCN*C*C), 55.46 (Ar*O*C), 74.76 (ArC_{ring}), 114.37, 129.28, 126.04, 132.07 (Ar), 180.30 (C=S). IR (ν/cm^{-1}): 1060, 1132, 1168, 1356, 1440, 1508, 1612. MS, *m*/*z* (%): 266 (M, 6), 190 (M – CS_2, 60), 121 [M – CS_2 – $N_2C_3H_5$(ring), 100], 76 (CS_2 or C_6H_4, 86).

*3-(4-Methylphenyl)dihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole-1-thione* **5d**: R_f 0.72 [*n*-hexane–ethyl acetate, 2:1 (v/v)], mp 110.0–110.5 °C. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, Me), 2.55 (m, 2H, NCH_2CH_2, ^2J 9.8 Hz, ^3J 4.9 Hz), 2.75, 3.15 (2m, 2H, $ArCNCH_2$, ^2J 9.9 Hz, ^3J 5.2 Hz, $\Delta\nu$ 74.5 Hz), 3.78, 3.93 (2m, 2H, $SCNCH_2$, ^2J 9.9 Hz, ^3J 5.2 Hz, $\Delta\nu$ 38.7 Hz), 5.75 (s, 1H, SCH), 6.80, 7.50 (2d, 4H, $C_{Ar}H$, ^3J 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.25 (MeAr), 27.56 (NCH_2C), 45.81 (SCN*C*C), 51.29 (ArCN*C*C), 74.67 (ArC_{ring}), 127.72, 129,74, 131.34, 139.78 (Ar). IR (ν/cm^{-1}): 1060, 1132, 1172, 1352, 1444, 1504. MS, *m*/*z* (%): 250 (M, 60), 173 (M – CS_2 – H, 100), 105 (MeC_6H_4CH, 30), 91 (MeC_6H_4, 32), 76 (CS_2, 12), 76 (C_6H_4, 17).

3,4-Bis(2-phenylethyl)-1,3,4-thiadiazolidine-2,5-dithione **6**: yield 30–35%, R_f 0.69 [*n*-hexane–ethyl acetate, 4:1 (v/v)], mp 159.5–160.5 °C. ^{1}H NMR ($CDCl_3$) δ: 3.05 (t, 4H, $ArCH_2$, ^3J 8.6 Hz), 4.33 (t, 4H, NCH_2, ^3J 8.6 Hz), 7.28 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ: 32.84 (Ph*C*), 50.88 (NCH_2), 127.67 (*p*-C_{Ar}), 128.75 (*m*-C_{Ar}), 129.19 (*o*-C_{Ar}), 135.89 (*ipso*-C_{Ar}), 180.96 (C=S). IR (ν/cm^{-1}): 1074, 1148, 1164, 1212, 1350, 1444, 1496, 1604. MS, *m*/*z* (%): 358 (M, 15), 254 [M – $Ph(CH_2)_2$ – H, 40], 104 ($PhCH_2CH$, 100), 91 ($PhCH_2$, 60).

For characteristics of **5b**, **5c** and **5e** see Online Supplementary Materials.

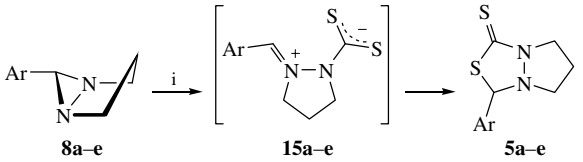
‡ 6-Aryl-1,5-diazabicyclo[3.1.0]hexanes **8a**,**d**,**e** were synthesised by the published method.[15] New compounds **8b**,**c** were obtained in the same way (see Online Supplementary Materials).

2-(4-Methylbenzylidene)pyrazolidin-2-ium-1-carbodithioate **15d**: R_f 0.42 [*n*-hexane–ethyl acetate, 2:1 (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H, Me), 0.55, 0.90 (2m, 2H, S^-CNCH_2), 1.55 (m, 2H, $NCCH_2$), 3.15, 3.60 (2m, 2H, N^+CH_2), 6.88, 7.81 (2d, 4H, $C_{Ar}H$, ^3J 9.7 Hz), 9.95 (s, 1H, Ar*CH*=N). ^{13}C NMR ($CDCl_3$) δ: 14.21 (*Me*Ar), 31.59 (NCH_2C), 48.36, 60.36 ($2NCH_2$), 129.62, 129.85, 134.20, 145.50 (Ar), 192.10 (Ar*C*H=N$^+$). Found (%): C, 57.65; H, 5.64; N, 11.05; S, 25.71. Calc. for $C_{12}H_{14}N_2S_2$ (%): C, 57.57; H, 5.64; N, 11.19; S, 25.61.

Table 1 Duration of the reaction and the yields of compounds **5**.

Compound	Ar	Reaction time/h	Yield of compound **5** (%)
8a	4-$MeOC_6H_4$	4	~99
8b	4-$EtOC_6H_4$	2	~99
8c	4-$Pr^iOC_6H_4$	4	~99
8d	4-MeC_6H_4	7	~99
8e	4-ClC_6H_4	7	30

solution, underwent gradual conversion into final bicyclic compound **5d**. Nevertheless, we performed elemental analysis and recorded the ^{1}H and ^{13}C NMR spectra of each of the compounds. The ^{1}H NMR spectra were similar to those obtained for the mixture of the corresponding compounds in the reaction of bicyclic compound **8a**. A comparison of the ^{13}C NMR spectra of compound **5d** and its precursor shows that both spectra contain the signals of carbon atoms of the pyrazolidine and benzene rings, but they are shifted downfield in the spectrum of the intermediate in comparison with that of compound **5d**. The spectrum of the latter contains a signal with a chemical shift of 180.7 ppm corresponding to the carbon atom of the C=S moiety and a signal with a chemical shift of 74.6 ppm corresponding to the CH moiety of the thiazolidine ring in compound **5d**. In the ^{13}C NMR spectrum of the intermediate, the signal of the CH moiety is shifted downfield (192.1 ppm), whereas the signal of the carbon atom in the C=S moiety is absent. Based on the spectral data and the easy conversion to give end product **5d**, it can be assumed that the structure of the intermediate is **15d** (Scheme 5). The absence of the signal of the carbon atom in the C=S moiety in assumed intermediate **15** is apparently due to electron density delocalisation between both sulfur atoms.



8a–e **15a–e** **5a–e**

Scheme 5 *Reagents and conditions*: i, CS_2 (excess), [bmim][BF_4] or [bmim][PF_6], $Et_2O{\cdot}BF_3$, 20 °C.

The structures of all the compounds obtained were confirmed by a combination of elemental analyses and spectral data, including those for compound **15d**; furthermore, X-ray diffraction analysis was carried out for compound **5d**.§

According to X-ray diffraction analysis, the pyrazolidine ring is characterised by an envelope conformation, where the C(6) atom deviates by 0.59 Å from the plane of the rest of the atoms. In turn, the sulfur-containing five-memebred ring has a distorted twisted conformation with deviations of the N(5) and C(4) atoms by 0.50 and 0.17 Å in opposite directions. The nitrogen atoms in **5d** differ significantly. Indeed, the N(1) atom is characterised by a planar trigonal configuration; in contrast, the N(5) atom has a pyramidal configuration with the sum of bond angles equal to 325.6(1)°. This drastic difference clearly

§ *X-ray diffraction data.* Crystals of **5d** ($C_{12}H_{14}N_2S_2$, M = 250.37) are monoclinic, space group $P2_1/c$, at 100(2) K: a = 14.8215(14), b = 7.4625(7) and c = 11.8230(10) Å, β = 112.039(5)°, V = 1212.13(19) Å^3, Z = 4, d_{calc} = = 1.372 g cm^{-3}, μ(MoKα) = 4.12 cm^{-1}, F(000) = 528. Intensities of 8641 reflections were measured with a Bruker Smart APEX II diffractometer (ω-scans, $2\theta < 58°$), 3178 independent reflections (R_{int} = 0.0378) were used in the further refinement. The refinement converged to wR_2 = 0.0886 and GOF = 0.990 for all independent reflections [R_1 = 0.0334 was calculated against F for 10362 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 671036 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

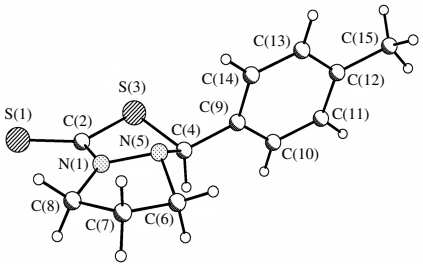


Figure 1 General view of a molecule of **5d**.

results from the conjugation of a lone electron pair at N(1) with the C=S bond. Note that the lone electron pairs at both S(1) and N(5) are antiperiplanar to the C(4)–H(4) bond; thus, one can suppose that the latter hydrogen atom has a considerable acidic nature.

Thus, this study allowed us to develop the synthesis of 3-(4-aryl)dihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole-1-thiones **5a–e** by $Et_2O{\cdot}BF_3$-catalysed CS_2 insertion into the C–N bond of the diaziridine ring in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **8a–e**. We found that this reaction requires ionic liquids to be used as the reaction medium. In the synthesis of compound **5d**, we succeeded in isolating and characterising intermediate **15d**, a direct precursor of the end product.

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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.2008.01.016.

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