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Mendeleev Commun., 2008, **18**, 207–208

Mendeleev Communications

Diaziridine ring expansion in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes on treatment with nitriles assisted by ionic liquids

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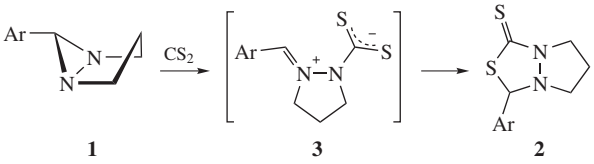
DOI: 10.1016/j.mencom.2008.07.013

The ionic-liquids-assisted insertion of activated nitriles into the diaziridine ring of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes catalysed with $BF_3{\cdot}Et_2O$ provides a simple method for the preparation of 1-aryl-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2,4]triazoles.

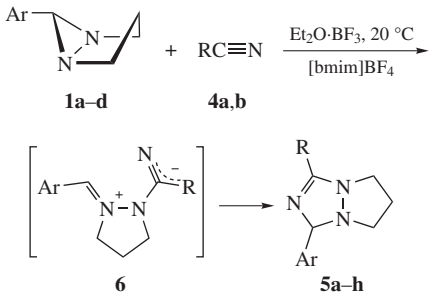
Reactions of diaziridines with ring expansion on treatment with electrophilic reagents are known; however, the majority of compounds studied so far belong to N-unsubstituted diaziridines.[1–3] We found that these reactions are also possible for N,N′-disubstituted diaziridines (both mono- and bicyclic) with sufficiently reactive electrophilic reagents (ketenes, aroylisocyanates and aroylisothiocyanates, but not CS_2).[4–8] Recently,[9] we found conditions for the efficient insertion of CS_2 into the CN bond of the three-membered ring in bicyclic diaziridines **1**. The insertion of CS_2 into the C–N bond of the diaziridine ring requires ionic liquids to be used as a reaction medium and $Et_2O{\cdot}BF_3$ as a catalyst. These reactions starting from 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **1** gave 3-aryldihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]-thiadiazole-1-thiones **2**; the yields were nearly quantitative for compounds **2** containing electron-donating substituents at the 4-position of the aryl substituent (Scheme 1). NMR spectroscopy revealed the formation of dipolar intermediates **3**, *i.e.* precursors of products **2**; intermediate **3** with Ar = 4-MeC_6H_4 was isolated and characterised (Scheme 1).



Scheme 1

Here we report the reactions of 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **1a–d** with insufficiently electrophilic reagents, *viz.*, nitriles **4a**,**b**. Numerous attempts to perform these reactions in ordinary organic solvents, including those catalysed by $Et_2O{\cdot}BF_3$, failed: in all cases, complex inseparable mixtures of at least seven compounds were formed. However, when an ionic liquid ([bmim][BF_4]) was used as the solvent, $Et_2O{\cdot}BF_3$ was used as the catalyst and the reaction was carried out at 20 °C, the expected result was achieved, namely, target 6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2,4]triazoles **5a–h** were obtained in all cases (Scheme 2). The molar ratio between starting compounds **1** and **4** was 1:1.3–1.5. The completion of the reaction was judged from the full conversion of starting bicyclic diaziridines **1** (TLC monitoring).

The reaction time depended on the substituents in starting bicyclic diaziridines **1** and nitriles **4** used in the reaction (see Table 1). The reactivity of the starting bicycles decreased in the order **1b** ≥ **1a** > **1c** > **1d**, and that of nitriles decreased in the



Scheme 1

order **4b** > **4a**. The syntheses of compounds **5e**,**f** containing strong electron-donating substituents at the aromatic ring of starting compounds **1a**,**b** and a strong electron-withdrawing substituent in starting nitrile **4b** took 30 min, whereas the reaction of diaziridine **1a** with nitrile **4a** containing a weaker electron-withdrawing substituent was completed in 18 h. The reactions of bicyclic diaziridines **1c**,**d** with nitrile **4a** at 20 °C occurred so slowly that only due to the temperature increase up to 70 °C the reaction could be completed in 20 h in both cases. Attempts to use 6-aryl-1,5-diazabicyclo[3.1.0]hexane containing an electron-withdrawing substituent at the aromatic fragment (4-ClC_6H_4) did not result in reactions with any of nitriles **4a**,**b**.

Table 1 Reactions of diaziridines with nitriles.

Starting compounds		Reaction time/h	Product	Yield (%)
Diaziridine	Nitrile			
1a	**4a**	18	**5a**	43
1b	**4a**	11	**5b**	40
1c	**4a**	20[a]	**5c**	45
1d	**4a**	20[a]	**5d**	37
1a	**4b**	0.5	**5e**	~99
1b	**4b**	0.5	**5f**	~99
1c	**4b**	1	**5g**	82
1d	**4b**	5	**5h**	83

[a]At 70°C.

The yields of 1-aryl-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2,4]-triazoles **5a–h** also depended on the substituents in the starting compounds, mainly in nitriles **4** (see Table 1). The smallest yields of compounds **5** (≤ 45%) were observed in reactions with nitrile **4a**. Formation of polymeric products was observed in these cases. Compounds **5e**,**f**, *i.e.* reaction products of nitrile **4b** and diaziridines **1a**,**b**, were obtained in the highest yields (~99%).

TLC monitoring of the reactions showed that one more compound with a smaller R_f was formed in addition to end products **5**; this compound disappeared when the process approached completion. It was assumed that this compound was dipolar intermediate **6** similar to intermediate **3**, which was found previously[9] in the reaction of 6-aryl-1,5-diazabicyclo[3.1.0]-hexanes with CS_2 (Scheme 1). The NMR spectra of the isolated reaction products of diaziridines **1a–d** with nitrile **4a** contained no signals of the intermediate product; however, the ^{1}H and ^{13}C NMR spectra† of the reaction products of diaziridines **1a–d** with nitrile **4b** showed the presence of ~10% of intermediates **6**. The most characteristic feature of the ^{1}H NMR spectra of compounds **5** and **6** is the position of the signal of the proton at the carbon atom bound to the aromatic fragment: for compounds **5e–h**, it manifests itself as a singlet at δ 5.20–6.00 ppm, whereas for corresponding intermediates **6e–h**, it appears in the region δ 9.80–10.0 ppm. A similar picture is observed in the ^{13}C NMR spectra: in compounds **5e–h**, this carbon atom resonates in the region δ 86.00–87.50 ppm, whereas in compounds **6e–h**, in the region δ 190.00–192.00 ppm. These differences in the NMR spectroscopic characteristics of intermediates and products agree with the differences found[9] for dipolar intermediate **3**. Attempts to isolate individual intermediates **6e–h** failed: the column chromatography of mixtures of compounds **5e–h** and **6e–h** resulted in the quantitative conversion of the latter to bicyclic compounds **5e–h**.

Thus, this study resulted in a discovery of a new reaction of diaziridine ring expansion. On this basis, a simple method was developed for obtaining 1-aryl-6,7-dihydro-1*H*,5*H*-pyrazolo-[1,2-*a*][1,2,4]triazoles **5a–h**, which involves $BF_3{\cdot}Et_2O$-catalysed insertion of the CN group of nitriles **4a**,**b** into the diaziridine ring of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **1a–d** with the use of ionic liquids as the reaction medium.

Heterocyclic systems incorporating the 6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2,4]triazole framework have been reported in the literature, but their syntheses require multistage processes and more complex starting compounds.[10,11] Heterocyclic structures containing the 1,2,4-triazole ring fused with other heterocyclic systems are of interest as inhibitors of NO synthase and as antidiabetic agents.[12,13]

This work was supported in part by the Presidium of the Russian Academy of Sciences (the programme 'Development of Methods for Synthesising Chemical Compounds and Creating New Materials').

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.07.013.

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Received: 11th December 2007; Com. 07/3058

† All 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 Bruker AC-200-31 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) and Bruker AM-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) spectrometers ($CDCl_3$ was used as an internal standard). ^{13}C NMR spectra were recorded under proton decoupling conditions. The signals in the ^{13}C NMR spectra of compounds **5** were assigned using {^{1}H-^{1}H}NOESY, {^{1}H-^{13}C}HMBC and {^{1}H-^{13}C}HSQC on Bruker DRX500 (500 MHz for ^{1}H and 126 MHz for ^{13}C) for compound **5a** as an example. Mass spectra were measured on a Finnigan MAT INCOS-50 instrument. TLC was carried out on Silufol UV-254 plates. R_f [*n*-hexane–ethyl acetate, 2:1 (v/v)]. Melting points were measured on a Gallenkamp instrument (Sanyo). 6-Aryl-1,5-diazabicyclo[3.1.0]hexanes **1a–d** were synthesised by a published method.[14]

*Ethyl 1-(4-methoxyphenyl)-6,7-dihydro-1*H,*5*H*-pyrazolo[1,2-*a*][1,2,4]-triazole-3-carboxylate* **5c**: nondistilled oil, R_f 0.30. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, 3H, $COOCH_2Me$, ^3J 7.39 Hz), 1.98, 2.34 (2m, 2H, NCH_2CH_2, ^2J 11.10 Hz, $\Delta\nu$ 68.96 Hz), 3.03 (m, 2H, CH_2NC=N, ^2J 13.78 Hz), 3.72 (m, 2H, CH_2N–N, ^2J 8.96 Hz), 3.77 (s, 3H, *Me*OAr), 4.14 (q, 2H, $COOCH_2$Me, ^3J 7.39 Hz), 5.28 (s, 1H, ArC*H*N), 6.88, 7.47 (2d, 4H in Ar, ^3J 8.95 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.43 (*Me*CH_2OCO), 24.92 ($CH_2CH_2CH_2$), 46.46 (CH_2N–N), 55.27 (CH_2NC=N), 60.35 (*Me*OAr), 61.99 (MeCH_2OCO), 62.37 (Ar*C*HN), 114.15, 124.29, 129.55, 146.59 (Ar), 157.15 (NC=N), 160.25 (OC=O).

*1-(4-Methoxyphenyl)-3-(trichloromethyl)-6,7-dihydro-1*H,*5*H*-pyrazolo-[1,2-*a*][1,2,4]triazole* **5g**: nondistilled oil, R_f 0.58. ^{1}H NMR ($CDCl_3$) δ: 2.08 (m, 2H, NCH_2CH_2, ^2J 12.24 Hz), 2.61, 2.98 (2br. m, 2H, CH_2NC=N, $\Delta\nu$ 81.60 Hz), 3.65, 4.03 (2br. m, 2H, CH_2N–N, $\Delta\nu$ 85.70 Hz), 3.72 (s, 3H, *Me*OAr), 5.88 (s, 1H, ArC*H*N), 6.85, 7.36 (2d, 4H in Ar, ^3J 8.16 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.60 ($CH_2CH_2CH_2$), 46.93 (CH_2N–N), 50.40 (br., CH_2NC=N), 55.05 (*Me*OAr), 87.12 (br., Ar*C*HN), 88.49 (CCl_3), 113.69, 127.86, 130.67, 159.37 (Ar), 162.32 (NC=N). MS, *m*/*z* (%): 334 (M, 17), 264 (M – pyrazolidine, 12), 229 (M – $MeOC_6H_4$, 95), 144 (Cl_3CCN, 100), 92 (OC_6H_4, 45), 76 (C_6H_4, 75), 71 ($C_3H_7N_2$, 10).

*1-(4-Methylphenyl)-3-(trichloromethyl)-6,7-dihydro-1*H,*5*H*-pyrazolo-[1,2-*a*][1,2,4]triazole* **5h**: nondistilled oil, R_f 0.77. ^{1}H NMR ($CDCl_3$) δ: 2.11 (m, 2H, NCH_2CH_2, ^2J 14.04 Hz), 2.39 (s, 3H, *Me*Ar), 2.68, 3.05 (2br. m, 2H, CH_2NC=N, $\Delta\nu$ 102.08 Hz), 3.69, 4.08 (br. m, 1H, CH_2N–N, $\Delta\nu$ 127.60 Hz), 5.98 (s, 1H, ArC*H*N), 7.19, 7.39 (2d, 4H in Ar, ^3J 6.38 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.10 (*Me*Ar), 24.68 ($CH_2CH_2CH_2$), 47.01 (CH_2N–N), 50.72 (br., CH_2NC=N), 87.46 (br., Ar*C*HN), 88.40 (CCl_3), 126.63, 129.08, 137.83 (Ar), 162.43 (NC=N).

Intermediate **6g**: R_f 0.46. ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 3H, *Me*OAr), 6.95, 7.79 (2d, 4H in Ar, ^3J 8.16 Hz), 9.85 (s, 1H, ArC*H*=N). ^{13}C NMR ($CDCl_3$) δ: 55.36 (*Me*OAr), 114.14, 131.74 (Ar), 162.80 (NC=N), 190.49 (Ar*C*HN).

Intermediate **6h**: R_f 0.62. ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H, *Me*Ar), 7.32, 7.78 (2d, 4H in Ar, ^3J 6.38 Hz), 9.95 (s, 1H, ArC*H*=N). ^{13}C NMR ($CDCl_3$) δ: 20.96 (*Me*Ar), 29.59 ($CH_2CH_2CH_2$), 36.40 (CH_2N–N), 60.26 (br., CH_2NC=N), 171.10 (NC=N), 191.85 (Ar*C*HN).

For spectral characteristics of compounds **5a**,**b**,**d–f** and **6e**,**f** see Online Supplementary Materials.