Thiadiazolium ylides: Substituted 2*H*-1,3,5-thiadiazines and 1,4,5-trisubstituted-imidazoles from 1,2,4- and 1,2,5-thiadiazolium-2-unsubstituted methanide (ylide) systems: ring expansions and ring interconversions *via* sulfur-nitrogen heterotriene intermediates. Mechanistic *ab initio* calculations. Azolium 1,3-dipoles

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Quaternisation of 3,5-diaryl-1,2,4-thiadiazoles with trimethylsilylmethyl triflate at 40 °C occurred at N-2. Separate desilylation of the salts resulted in a ring expansion to substituted 2*H*-1,3,5-thiadiazines **5**. Heating of these with ethanolic sodium ethoxide caused sulfur extrusion and ring contraction to 2,4-disubstituted imidazoles **6**. 3,4-Diaryl-1,2,5-thiadiazoles were less reactive to alkylation and trimethylsilylmethylation required heating at 80 °C. Treatment of the salts with CsF unexpectedly gave 1-trimethylsilylmethyl-4,5-diarylimidazoles **21**. ^{1}H, ^{13}C, ^{15}N NMR spectra are described and the mechanisms were studied by *ab inito* calculations with the GAUSSIAN94 series of programmes using the HF/6-31G* theoretical level.

Exocyclic azolium unsubstituted methanide 1,3-dipoles can be generated from azolium *N*-trimethylsilylmethyl triflate salts by treatment with CsF,[1–3] following a literature procedure developed[4,5] with Schiff bases. We have recently generated[1–3] the oxadiazole and triazole species **11** and **12** (see Scheme 2). When it is valency-allowed these unstable intermediates rapidly ring-open and recyclise *via* a 1,3,5-heterotriene.[1–3] *Ab initio* calculations showed a large free energy fall and low activation energies for this rearrangement.[2] The reaction with the species **11** (from **8**) provided a route to the 1,2,5-oxadiazine ring which despite earlier misconceptions is not well-known.[6]

Renewed interest in the chemistry of organo-sulfur systems[7–9] prompted us to explore the influence of sulfur and to extend this work into the full thiadiazole series. Herein we report the behaviour of the 1,2,4- and 1,2,5-thiadiazolium unsubstituted methanides species **3** and **13** respectively. Valency permitted ring-opening of these would result in the heterotrienes **4** and **16** containing C=S and N=S moieties. In the event desilylation of the salts **2** and **10** gave new routes to 2*H*-1,3,5-thiadiazines **5** and 1,4,5-trisubstituted imidazoles **21** respectively. New routes to 2-unsubstituted imidazoles are still of interest because of the pharmaceutical importance of the system.[10] Recently we have reported[11] the *N*-methanides of the 1,3,4-thiadiazole system where ring-opening to hetero-1,3,5-trienes is not valency permitted and the ylides behaved as new 1,3-dipoles giving cycloaddition rearrangement sequences.[11] In a forthcoming paper we will complete the thiadiazole series with the 1,2,3-thiadiazole case. We are particularly interested in the unsubstituted methanide series, rather than more amenable cases bearing stabilising electron withdrawing groups, since these unsubstituted methanides are the carbon analogues of the azole *N*-oxides.

Results and discussion

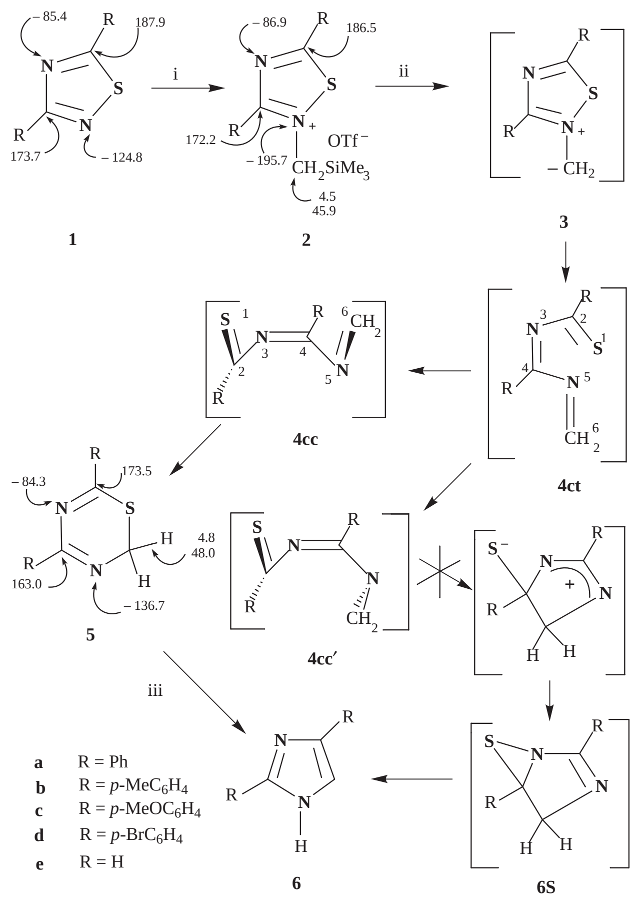
(a) 1,2,4-Thiadiazoles

Alkylation of the 1,2,4-thiadiazole series **1** with trimethylsilylmethyl trifluoromethanesulfonate at 40 °C in CH_2Cl_2 occurred at N-2 giving the compounds **2** (Scheme 1, Table 1). The structure of these was established from microanalyses, IR, ^{1}H, ^{13}C and ^{15}N NMR spectra showing all of the expected signals, as well as their subsequent reactions. The ring ^{13}C shifts of the quaternised compounds **2** showed small shielding shifts as expected[12] relative to the parent molecules **1** but the changes were too small to be of structural diagnostic value other than

Table 1 Substrates and products

Entry	Compound (Substrate)	Mp (T/°C)	Yield (%)	Compound (Product)	Mp (T/°C)	Yield (%)
1	**2a**	151[a]	79	**5a**	93–94[e]	81
2	**2b**	143–144[a]	73	**5b**	111–112[e]	76
3	**2c**	—[b]	76	**5c**	149–150[e]	71
4	**2d**	—[c]	—[c]	**5d**	142–143[e]	66[f]
5	**7a**	83–85[d]	42	**21a**	120–121[d]	24
6	**7b**	107–108[d]	20	**21b**	120–121[d]	21
7	**7c**	98–100[d]	33	**21c**	118–119[d]	26
8	**7d**	130–132[d]	27	**21d**	107–108[d]	20
9	**5a**	93–94[e]	81	**6a**	168	69
10	**5c**	149–150[e]	71	**6c**	185	65

[a] From CH_2Cl_2–Et_2O. [b] Unstable in air, used immediately. [c] Not isolated, used *in situ*. [d] From hexane. [e] From CH_2Cl_2–hexane. [f] Yield over two steps from **1d**.



Scheme 1 *Reagents*: (i) Me_3SiCH_2OTf; (ii) CsF; (iii) NaOEt, heat. Some ^1H, ^{13}C, and ^{15}N NMR shifts shown for series a in $CDCl_3$.

agreeing with the overall structure. However quaternisation at N-2 was confirmed by the ^{15}N shifts which showed a shielding shift of >70 ppm (Scheme 1) at the quaternised N-atom adjacent to sulfur. Similar effects have been observed [13] for *N*-alkyl quaternisation of other sulfur azoles. The stability of the salts **2** depended on the substituents R and compound **2c** had to be used immediately on isolation while compound **2d** decomposed on attempted purification and had to be reacted *in situ* (Table 1).

When the salts **2** were desilylated with CsF [4,5] the expected 1,3-dipoles **3** could not be trapped with alkyne or alkene dipolarophiles. Instead the 2*H*-1,3,5-thiadiazines **5** were isolated in good yields (Table 1). The structures of these products were established from microanalyses as well as ^1H, ^{13}C and ^{15}N NMR spectra which showed all of the expected signals (Scheme 1). A significant feature of these molecules is the unsubstituted methylene group between S-1 and N-3. When heated with ethanolic sodium ethoxide the thiadiazines extruded sulfur and ring-contracted to the 2,4- disubstituted imidazoles **6** but under normal conditions they were stable in solution. By comparison with our earlier results for triazoles and oxadiazoles [1–3] we interpret this ring expansion as progressing through the unstable intermediates **3** and **4** the latter of which gives the products **5** by a bond rotation to **4cc** and a 1,6-heteroelectrocyclisation.[14] In a related type of reaction with *N*-alkylthiazolium salts containing a stabilising electron withdrawing substituent in the *N*-alkyl group a ring-expansion to 2*H*-1,3-thiazines was found to proceed through a stable heterotriene intermediate.[15,16] The reactions **3e** through **4e** to **5e** were studied (*i.e.* with H-atoms at all sites) using *ab initio* molecular orbital methods including frequency calculations to ensure verifying transition state structures. All calculations were performed with the GAUSSIAN94 series of programs [17] using the HF/6-31G* theoretical level. Structure **3** was found to open to structure **4** where the C=S bond is nearly perpendicular to the rest of the molecule. Attempts to find a near planar structure for **4** all proved fruitless. There are two possible routes from **4** which involve rotation around the single $C^4–N^5$ bond pictured in Scheme 1. One involves the CH_2 group rotating up to meet the S atom out of the CNCN plane to form **5**. On the way structure **4** passes through a transition state (TS) to a *cis*, *cis* intermediate (**4cc**), then through another TS which leads to **5** (the term *cis*, *cis* refers to the rotational isomers of the single 2–3 and 4–5 bonds respectively throughout, *cf.* the Experimental section). The other route has the rotation in the opposite direction passing through an equivalent *cis*, *cis* intermediate (**4cc′**) and corresponding TS structures where the CH_2 group bonds upwards to the C atom of the CS group ultimately giving structure (**6S**) which is a [3.1.0] bicyclic compound. The energetics for these reactions are in Table 2 where the energies and entropies are given relative to structure **3**. There is a substantial barrier between **4cc′** and **6S** which precludes this route compared to that leading to structure **5**.

Table 2 Reaction energetics for Scheme 1 (relative to structure **3** for the **e** series)

Structure	ΔE/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}	ΔH/kcal mol^{-1}	ΔG/kcal mol^{-1}
3	0.0000	0.000	0.00	0.00
TS (**3** to **4**)	6.9455	−1.000	6.38	6.67
4	−47.6586	7.245	−46.31	−48.47
TS (**4** to **4cc**)[a]	−46.5470	3.765	−45.84	−46.97
4cc	−47.3714	6.577	−45.92	−47.88
TS (**4cc** to **5**)	−33.6156	1.334	−32.91	−33.31
5	−63.1668	−0.676	−60.63	−60.42
TS (**4** to **4cc′**)	−44.4633	3.820	−43.80	−44.94
4cc′	−45.7206	6.426	−44.31	−46.22
TS (**4cc′** to **6S**)	27.1393	−1.133	26.92	27.25
6S	−39.5721	−2.459	−37.08	−36.34

[a] For cc notation see the Experimental section.

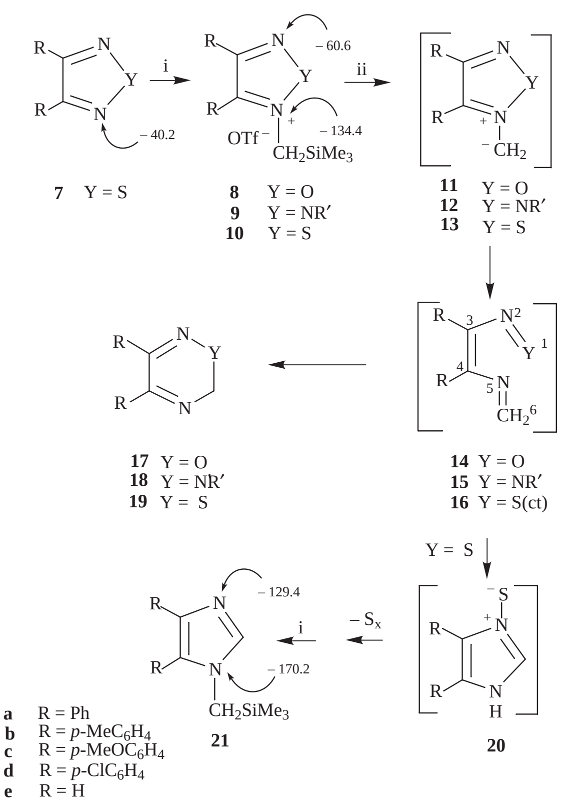
(b) 1,2,5-Thiadiazoles

The 1,2,5-thiadiazoles **7** proved to be less reactive than the 1,2,4-isomers **1** when treated with trimethylsilylmethyl triflate. Heating at temperatures of 80 °C for 12 h with 2.5 mol of the reagent as solvent was necessary to achieve complete alkylation to give the salts **10** as gummy residues. Treatment with CsF in CH_2Cl_2 unexpectedly gave the imidazoles **21** (<30%) and decomposition resins. The structures of the products **21** were indicated by ^1H and ^{13}C NMR spectra which showed all of the expected signals. These structures were proved by unequivocal synthesis of the 4,5-diarylimidazoles [18] followed by separate alkylation with trimethylsilylmethyl trifluoromethanesulfonate giving the same compounds **21**. We interpret the formation of the products **21** as shown in Scheme 2. It is likely that the expected ylides **13** were formed from the salts **10** and they should behave as did the oxygen and nitrogen analogues **11** and **12**. For example with the triazole case **12**, ring opening to **15** gave a mixture of 1-aminoimidazoles and the triazines **18**.[3] The precursor to the 1-aminoimidazole product was the species **20** (N^-R' for S^-) which aromatised to the 1-aminoimidazole by a 1,3-H shift. With the sulfur system the intermediate **20** should lose sulfur leading to the final product **21** which can arise by *in situ* alkylation of the imidazole with the excess unreacted trimethylsilylmethyl triflate. The possible 1,2,5-thiadiazine **19** could not be found in these reactions although it could have been formed and also given rise to the 4,5-diarylimidazoles by ring-contraction with sulfur extrusion. The calculations (Table 3) suggest that the reactions **13** through **16** to **19** and to **21** are different from those found for the 1,2,4-thiadiazole reaction. Structure **16** was found to be nearly planar. This means that rotation of the $N{=}CH_2$ group will lead to the six-membered ring

Table 3 Reaction energetics for Scheme 2 (relative to structure **13** for the e series)

Structure	Δ*E*/kcal mol^{-1}	Δ*S*/cal mol^{-1} K^{-1}	Δ*H*/kcal mol^{-1}	Δ*G*/kcal mol^{-1}
13	0.000	0.000	0.00	0.00
TS (**13** to **16ct**)[a]	15.9071	−0.765	15.27	15.50
16ct	−1.9909	5.508	−1.65	−3.29
TS (**16ct** to **tt**)	0.9484	2.987	0.50	−0.39
16tt	−7.4954	5.799	−7.07	−8.80
TS (**16tt** to **tc**)	−5.5680	2.710	−5.88	−6.69
16tc	−9.1171	4.869	−8.64	−10.09
TS (**16c** to **20**)	4.8605	0.276	4.41	4.33
20	−42.0447	−0.792	−39.83	−39.59
TS (**16ct** to **cc**)	0.8266	3.018	0.51	−0.39
16cc	0.6639	5.863	1.02	−0.72
TS (**16cc** to **19**)	5.0036	0.458	4.54	4.40
19	−41.3830	−0.702	−39.85	−39.64

[a] For ct notation see the Experimental section.



Scheme 2 *Reagents*: (i) Me_3SiCH_2OTf; (ii) CsF. ^{15}N shifts for **7a**, **10a** and **21a** shown.

19 while rotation of both the N=CH$_2$ and N=S groups leads to **20**. Defining **16** as the *cis*, *trans* configuration (**16ct**), structure **16** goes to **19** by passing through a *cis*, *cis* intermediate, or **16** goes to **20** by passing through a *trans*, *trans* then a *trans*, *cis* intermediate, (*cf.* the Experimental section). The energetics (Table 3) are such that the two routes are competitive. In any case, loss of sulfur from **19** or **20** can each be expected to give **21** under these conditions. Table 3 gives the energies and entropies relative to structure **13**. Also of interest from the calculations is the result that ring-opening of the 1,2,5-thiadiazolium ylide **13** has a significantly higher activation barrier than that for the 1,2,4-isomer **3**.

Experimental

Mps were measured on an Electrothermal apparatus. The 3,5-diaryl-1,2,4-thiadiazoles **1** were prepared by treating thiobenzamide with butyl nitrite following a literature procedure[19] and the 1,2,5-thiadiazoles **7** were obtained from the reaction of the corresponding diaryl acetylenes, prepared by oxidation of *p*-substituted benzil bishydrazones,[20] with S_4N_4.[21] NMR spectra were measured on a JEOL LAMBDA 400 MHz instrument with tetramethysilane as reference for ^{13}C and proton shifts and nitromethane for ^{15}N shifts. IR spectra were measured on a Perkin-Elmer 983G spectrophotometer and microanalyses were measured on a Perkin-Elmer model 240 CHN analyser. The following examples show typical experimental procedures:

(ia) 3,5-Diphenyl-2-trimethylsilylmethyl-1,2,4-thiadiazol-2-ium trifluoromethanesulfonate (2a) (Table 1, entry 1)

A solution of 3,5-diphenyl-1,2,4-thiadiazole (1.0 g, 4.5 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (1.8 cm^3, 9.0 mmol) in dry CH_2Cl_2 (5 cm^3) was stirred at 40 °C under a reflux condenser for 24 h, evaporated under reduced pressure and the white residue washed with diethyl ether to give the compound **2a**, mp 151 °C (from CH_2Cl_2–Et_2O) (79%) (Found: C, 47.6; H, 4.1; N, 5.9. $C_{19}H_{21}F_3N_2O_3S_2Si$ requires C, 48.0; H, 4.4; N, 5.9%); δ_H (CD_2Cl_2) 0.1 (s, 9H, SiMe$_3$), 4.5 (s, 2H, CH$_2$-N), 7.6–7.8 (m, 6H, H$_{meta,\ para}$, Ph), 7.95–7.97 (m, 2H, H$_{ortho}$, Ph), 8.10–8.12 (m, 2H, H$_{ortho}$, Ph); δ_C (CD_2Cl_2) −2.1 (SiMe$_3$), 45.9 (N-CH$_2$), 186.5, 172.2 (C-5 and C-3), 128.2, 126.2 (C-1′ of 3-C-Ph and 5-C-Ph), 130.4, 129.5 (C-3′ of 3-C-Ph and 5-C-Ph), 130.9 and 130.8 (C-2′ of 3-C-Ph and 5-C-Ph), 136.8, 134.5 (C-4′ of 3-C-Ph and 5-C-Ph); δ_N (in $CDCl_3$ from CH_3NO_2) −195.7 (N-2), −86.9 (N-4).

(ib) 4,6-Diphenyl-2*H*-1,3,5-thiadiazine (5a)

A solution of **2a** (0.47 g, 1.02 mmol) in dry dichloromethane (10 cm^3) was treated with CsF (300 mg, 2 mmol), stirred at ambient temperature for 24 h, filtered to remove salts and then evaporated under reduced pressure. The residue in dichloromethane (2 cm^3) was placed on a silica gel-60 column (70–230 mesh ASTM). Elution with methylene chloride gave compound **5a** (81%) mp 93–94 °C (from CH_2Cl_2–hexane 1:1 v/v) (Found: C, 71.2; H, 5.0; N, 11.2. $C_{15}H_{12}N_2S$ requires C, 71.3; H, 4.8; N, 11.1%); ν_{max} (mull) 1602.9, 1571.9 cm^{-1} C=N; δ_H ($CDCl_3$) 4.8 (s, 2H, SCH$_2$N), 7.4–7.6 (m, 6H, H$_{meta,\ para}$, Ph), 8.2–8.3 (m, 4H, H$_{ortho}$, Ph); δ_C ($CDCl_3$) 48.0 (SCH$_2$N), 163.0 (C-4), 173.5 (C-6), 137.2, 136.4 (C-1′ of 4-Ph and 6-Ph), 129.0, 128.9 (C-2′ of 4-Ph and 6-Ph), 128.4, 128.1 (C-3′ of 4-Ph and 6-Ph), 133.5, 131.1 (C-4′ of 4-Ph and 6-Ph); δ_N (in $CDCl_3$ from CH_3NO_2) −84.3 and −136.7, N-5 and N-3.

3,5-Diphenyl-1,2,4-thiadiazole (19%) was also recovered from the column.

(ii) 4,6-Bis(*p*-bromophenyl)-2*H*-1,3,5-thiadiazine (5d) (Table 1, entry 4)

A solution of 3,5-bis(*p*-bromophenyl)-1,2,4-thiadiazole (0.5 g, 1.26 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (0.5 cm^3, 2.5 mmol) in chlorobenzene (10 cm^3) was heated at 80 °C for 24 h. The resultant mixture was cooled to ambient temperature, treated with CsF (0.38 g, 2.5 mmol) stirred for 24 h and filtered to remove salts. After evaporation under reduced pressure the solution was placed on a column of silica gel-60 (70–230 mesh ASTM). Elution with dichloromethane gave **5d**, mp 142–143 °C (from CH_2Cl_2–hexane) (0.34 g, 66%) (Found: C, 43.8; H, 2.3; N, 6.6. $C_{15}H_{10}Br_2N_2S$ requires C, 43.9; H, 2.45; N, 6.8%); ν_{max} (mull) 1601.5, 1587.9 cm^{-1} (C=N); δ_H ($CDCl_3$) 4.8 (s, 2H, SCH$_2$N), 7.55, 8.09 (4H, ds, AA′BB′, J_{AB} 8.7 Hz), 7.63, 8.02 (4H, ds, J_{AB} 7.8 Hz), two *p*-BrC$_6$H$_4$; δ_C ($CDCl_3$) 48.0 (SCH$_2$N), 172.7, 161.9 (C-6, C-4), 135.9, 135.2 (C-1′ of 4-Ar, 6-Ar), 132.2, 131.6 (C-2′ of 4-Ar, 6-Ar), 130.2, 129.6 (C-3′ 4-Ar, 6-Ar), 128.6, 125.9 (C-4′ of 4-Ar, 6-Ar). 3,5-Bis(*p*-bromophenyl)-1,2,4-thiadiazole (20%) was also eluted from the column.

(iii) 1-Trimethylsilylmethyl-4,5-diphenyl-1*H*-imidazole (21a) (Table 1, entry, 5)

A solution of 3,4-diphenyl-1,2,5-thiadiazole (0.3 g, 1.26 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (0.63 cm^3, 3.15 mmol) was stirred at 80 °C for 12 h and cooled to give a residue containing the salt **10a**, δ_H ($CDCl_3$) 0.2 (s, 9H, $SiMe_3$), 4.0 (s, 2H, CH_2-N), 7.0–7.3 (m, 10H, Ph); δ_C ($CDCl_3$) −1.3 ($SiMe_3$), 39.0 (N-CH_2), 160.8 (C-3), 159.7 (C-4), 118.1, 121.2 (C-1′ of 3-C-Ph and 4-C-Ph), 127.9, 128.6 (C-2′ of 3-C-Ph and 4-C-Ph), 130.6, 129.4 (C-3′ of 3-C-Ph and 4-C-Ph), 133.4, 131.1 (C-4′ of 3-C-Ph and 4-C-Ph); δ_N (in $CDCl_3$ from CH_3NO_2) −60.6 and −134.4, N-5 and N-2. This residue in dichloromethane (5 cm^3) was treated with CsF and stirred for 12 h at ambient temperature placed on a Merck silica gel column (70–230 mesh ASTM) and when eluted with gradient mixtures of dichloromethane–diethyl ether (1:0–1:1 v/v) gave the title compound **21a**, mp 120–121 °C (hexane) (24%) (Found: C, 74.2; H, 7.4; N, 9.0. $C_{19}H_{22}N_2Si$ requires C, 74.5; H, 7.2; N, 9.2%); δ_H ($CDCl_3$) 0.0 (9H, s, $SiMe_3$), 3.40 (2H, s, CH_2), 7.56 (1H, s, H-2), 7.13–7.50 (10H, m, Ph); δ_C ($CDCl_3$) −2.4 ($SiMe_3$), 36.1 (CH_2), 136.1 (C-2), 134.6 (C-5), 137.7 (C-4), 126.1, 126.4, 128.0, 128.5, 128.9, 130.9, 131.1 (aromatic CH), one signal not observed due to overlap in the 126–131 ppm region; δ_N ($CDCl_3$ from CH_3NO_2) −129.4 and −170.2, N-2 and N-1 respectively. Remaining resinous decomposition products were washed from the column with methanol as well as traces of 4,5-diphenylimidazole.

(iv) 2,4-Diphenyl-1*H*-imidazole (6a) (Table 1, entry 9)

A solution of 4,6-diphenyl-2*H*-1,3,5-thiadiazine **5a** (0.19 g, 0.753 mmol) in ethanol (5 cm^3) was treated with sodium ethoxide (0.09 g, 1.3 mmol), heated under reflux for 3 h, cooled and evaporated under reduced pressure and the residue in dichloromethane (2 cm^3) was placed on a silica gel-60 column (70–230 mesh ASTM). Elution with diethyl ether gave **6a**, mp 168 (lit.,[22] 168 °C) (from CH_2Cl_2–hexane) (0.11 g, 69%) (Found: C, 81.5; H, 5.2; N, 12.4. $C_{15}H_{12}N_2$ requires C, 81.7; H, 5.5; N, 12.7%); δ_H ($CDCl_3$) 7.3–7.7 (11H, m, Ar), 8.5 (1H, br s, NH).

Calculations

All calculations were carried out using the Gaussian94 series of programs.[17] The HF//6-31G* theoretical level was chosen for all structures. The nature of the stationary points on the potential energy surfaces were all identified using analytical second derivatives to compute vibrational frequencies. The normal mode of the single negative frequency obtained for transition state structures was inspected to insure that it connects the reactant and product of interest.

In order to keep track of the possible isomers a *cis–trans* notation was given for the rotations about the single C–N bonds. Upon opening from the five-membered thiadiazolo ring, single bonds are formed at the 2–3 and 4–5 positions of the resulting open chains and the rotational isomers are given a *cis* or *trans* designation in this respective order. Thus the first isomer to be formed upon ring opening is designated **ct**. The *trans* positions give a nearly planar component whereas the *cis* positions give a dihedral angle of *ca.* 60° about the appropriate single C–N bond.

Thus for example, in the reaction **3** to **4** the resulting isomer of **4** is **ct** (*i.e.* C^2–N^3 *cis* and C^4–N^5 *trans*). The *trans* N=CH_2 group can then rotate in a conrotatory direction relative to the *cis* S=C group going through the structure **4cc** to give **5**. A disrotatory direction goes through **4cc′** to give ultimately **6S** by attack on the C=S group by the terminal CH_2. In these two cases the S=C group remains *cis*. In the reaction of 1,2,5-thiadiazolo case, for the intermediate **16** the conrotatory rotation of the N–CH_2 group also leads to a six membered ring **19**. However, rotation of the N=S group may also occur before a disrotary rotation, forming a nearly planar **tt** structure. Subsequent rotation of the N–CH_2 group then ultimately gives rise to the structure **20** *via* a *trans*, *cis* intermediate.

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