pure **6a**, followed by a mixture of **6a** and **8a**, then pure **8a**, then a mixture of **8a** and **7a**, and finally pure **7a**. The compounds were recrystallized from ether, high-boiling ligroin, or ligroin–chloroform mixtures. Alcohol **7a** and tosylate **7b** gave mp 101–102 and 150–151 °C, respectively; alcohol **8a** and tosylate **8b** gave mp 102–103 and 180–181 °C, respectively.

Registry No.—**1a**, 61348-85-4; **1b**, 61348-86-5; **2a**, 61376-26-9; **2b**, 61376-27-0; **3a**, 61376-28-1; **3b**, 61376-29-2; **4a**, 61376-30-5; **4b**, 61376-31-6; **5a**, 61348-87-6; **5b**, 61348-88-7; **6a**, 61376-32-7; **6b**, 61376-33-8; **7a**, 61376-34-9; **7b**, 61376-35-0; **8a**, 61376-36-1; **8b**, 61376-37-2; **9**, 61348-89-8; **10**, 61348-90-1; **11**, 61348-91-2; **12**, 61348-92-3; *exo*-norbornene oxide, 3146-39-2; *p*-thiocresol, 106-45-6.

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Base-Induced Cycloaddition of Sulfonylmethyl Isocyanides to C,N Double Bonds. Synthesis of 1,5-Disubstituted and 1,4,5-Trisubstituted Imidazoles from Aldimines and Imidoyl Chlorides[1]

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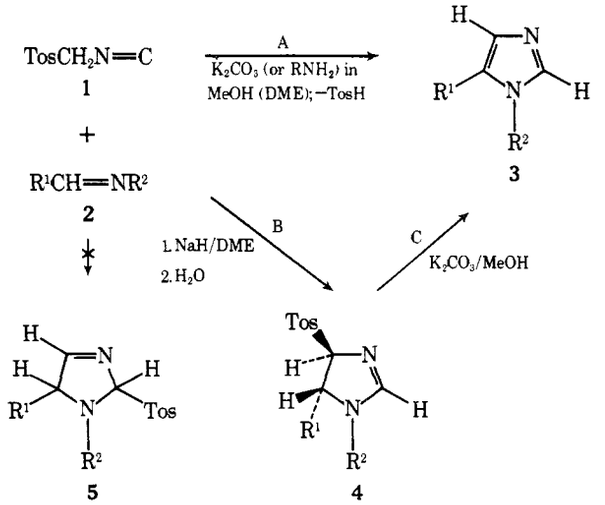
Base-induced cycloaddition of tosylmethyl isocyanide (TosMIC) to aldimines ($R^1CH{=}NR^2$) in protic medium occurs with concomitant elimination of *p*-toluenesulfinic acid to give the otherwise more difficultly accessible 1,5-disubstituted imidazoles (**3**). The influence of R^1 and R^2 on the formation of **3** is analyzed in a qualitative way. α-Tosylbenzyl isocyanide and α-tosylethyl isocyanide, likewise, give 1,4,5-trisubstituted imidazoles (**7**). The cycloaddition of TosMIC to imidoyl chlorides is accompanied by loss of HCl, instead of TosH, and leads to the 1,4,5-trisubstituted imidazoles **11**. Under aprotic conditions a number of *trans*-1,5-diaryl-4-tosyl-2-imidazolines (**4**) have been isolated and identified as the primary cycloadducts of TosMIC and aldimines, leading ultimately to the imidazoles **3**.

TosMIC (tosylmethyl isocyanide, **1**) is a new synthon of considerable utility. In previous communications we have shown its use in novel syntheses of a series of azoles[3] (including oxazoles,[3a] pyrroles,[3c] and 1,2,4-triazoles[3e]), and in the conversion of ketones to cyanides[4a] and to α-hydroxy aldehydes.[4b] The present paper is concerned with the application of TosMIC and some analogues to the synthesis of imidazoles (and 2-imidazolines) from aldimines or imidoyl chlorides.

Substituted imidazoles, many of which play an important role in biologically interesting processes, have been prepared by a variety of synthetic methods.[5] Although most substitution patterns can be realized by these methods, as yet no simple, straightforward synthesis of 1,5-disubstituted imidazoles is reported. A limited number of such 1,5-disubstituted imidazoles has been obtained previously by separation from a mixture of 1,4- and 1,5-disubstituted imidazoles formed by N-alkylation of 4(5)-aryl- or 4(5)-alkylimidazoles.[6]

Synthesis of 1,5-Disubstituted Imidazoles. The TosMIC molecule (**1**), which accommodates a reactive isocyanide carbon and an activated methylene,[7] can cycloadd its $CH_2N{=}C$ moiety to polarized double bonds under basic conditions.[3,4] When applied to aldimines (**2**, Scheme I), this type of reaction results in the formation of imidazoles **3** by

Scheme I. Synthesis of Imidazoles 3 and 2-Imidazolines 4 from Aldimines (2) and TosMIC (1)[a]



[a] For substituents R^1 and R^2 in **3** see Table I; the same abbreviation to a, b, etc., holds for **2**, **4** (and **5**).

Table I. 1,5-Disubstituted Imidazoles (3) from $R^1CH{=}NR^2$ (2) and TosMIC (1) According to Scheme I

Compd	R^1	R^2	Method	Base	Medium	Temp, °C	Time, h	Yield, %	Mp, °C
3a	p-$O_2NC_6H_4$	C_6H_5	A	K_2CO_3	MeOH/DME	20	16	82	164–165
3b	C_6H_5	p-$O_2NC_6H_4$	A	K_2CO_3	MeOH/DME	76	1	70	154–155
3b	C_6H_5	p-$O_2NC_6H_4$	A	K_2CO_3	MeOH/DME	20	3	34	154–155
3b	C_6H_5	p-$O_2NC_6H_4$	B[a] + C	NaH/K_2CO_3	DME/MeOH	−20/76	1/0.5	65[b]	154–155
3c	p-$O_2NC_6H_4$	p-$O_2NC_6H_4$	A	K_2CO_3	MeOH/DME	20	16	87	215 (dec)
3c	p-$O_2NC_6H_4$	p-$O_2NC_6H_4$	A	t-$BuNH_2$	DME	20	24	[c]	
3d	p-ClC_6H_4	p-ClC_6H_4	A	K_2CO_3	MeOH/DME	20	16	43	154–155
3d	p-ClC_6H_4	p-ClC_6H_4	B[a] + C	NaH/K_2CO_3	DME/MeOH	−20/76	3/0.5	40[b]	154–155
3e	C_6H_5	C_6H_5	B[a] + C	NaH/K_2CO_3	DME/MeOH	−20/76	3/0.5	56[b]	130–131
3e	C_6H_5	C_6H_5	A	K_2CO_3	MeOH/DME	20	70	[d]	
3f	p-$CH_3C_6H_4$	C_6H_5	B[a] + C	NaH/K_2CO_3	DME/MeOH	−20/76	3/0.5	19[b]	97–98
3g	CH_3	C_2H_5	A	t-$BuNH_2$	DME	20	20	70	Picrate 146–147
3g	CH_3	C_2H_5	A	K_2CO_3	MeOH	20	20	62[f]	
3h	$(CH_3)_3C$	CH_3	A	t-$BuNH_2$[e]	MeOH	20	72	96	Bp 95 (0.05 mm)
3h	$(CH_3)_3C$	CH_3	A	K_2CO_3	MeOH	20	20	~5[f]	
3h	$(CH_3)_3C$	CH_3	B	NaH	DME	−7	4.5	[d]	
3i	CH_3	$(CH_3)_3C$	A	t-$BuNH_2$	MeOH	20	20	94	42–44
3i	CH_3	$(CH_3)_3C$	A	t-$BuNH_2$	DME	20	20	90	42–44
3i	CH_3	$(CH_3)_3C$	A	K_2CO_3	MeOH	20	20	54	42–44
3j	CH_3	c-C_6H_{11}	A	c-$HexNH_2$	MeOH	20	17	96	Bp 110 (0.1 mm)
3k	$(CH_3)_2CH$	$(CH_3)_2CH$	A	i-$PrNH_2$	MeOH	20	16	75	Bp 70 (0.05 mm)
3l	C_6H_5	CH_3	A	K_2CO_3	MeOH/DME	0	60	10	94–95 (lit.[40] 96–97)[g]
3l	C_6H_5	CH_3	B	NaH	DME	−10	4.5	[d]	
3m	p-$CH_3C_6H_4$	CH_3	A	K_2CO_3	MeOH	20	20	37	64–65
3n	p-$O_2NC_6H_4$	CH_3	A	K_2CO_3	MeOH	20	16	14	166–167[h] (lit.[40] 171–172)
3n	p-$O_2NC_6H_4$	CH_3	A	t-$BuNH_2$	MeOH	20	100	[c]	

[a] Intermediate 2-imidazolines 4b,e,f were isolated and characterized; 4d was detected by ^1H NMR only. [b] Overall yields over reactions B + C; for yields of separate steps see Experimental Section. [c] No formation of imidazole observed on TLC. [d] No, or very little, imidazole or 2-imidazoline (4) observed on TLC, TosMIC largely decomposed (see text). [e] Reaction carried out with 4 equiv of imine 2 and 4 equiv of t-$BuNH_2$; yield of 3h is 60% when equimolar quantities were used. [f] Yield determined by ^1H NMR. [g] Mp of picrate 136–138 °C, lit.[40] 138–139 °C. [h] 3n was identical with an authentic sample[40] by mixture melting point, IR, and ^1H NMR.

elimination of p-toluenesulfinic acid (TosH) from intermediate 4-tosyl-2-imidazolines **4**. This provides the first direct and unambiguous synthesis of 1,5-disubstituted imidazoles (**3**). The actual results are summarized in Table I.

The imidazoles **3** can be prepared, at least in principle, by two different procedures, as is shown in Scheme I. The complete conversion to **3** is effected in a single operation by using K_2CO_3 (or t-$BuNH_2$) in a methanol–1,2-dimethoxyethane mixture (reaction A). Alternatively, a two-step procedure is possible, which involves isolation of the intermediate 4-tosyl-2-imidazolines **4**, using NaH in dimethoxyethane (DME) (reaction B), followed by elimination of TosH in a separate step (C) with K_2CO_3 in refluxing MeOH. The methods A and B + C are not always interchangeable, however, as appears from Table I; they rather are supplementary.

Most of the 1,5-diarylimidazoles (**3a–f**) were prepared by the one-step procedure (A), as well as the two-step method (B + C). However, for the 1,5-dialkylimidazoles (**3g–k**) and the 1,5-alkylarylimidazoles (**3l–n**) only method A was successful (note **3h** and **3l**).

K_2CO_3 was used with success in all reactions carried out by method A (except for **3e**). Higher yields were obtained, although only in the case of 1,5-dialkylimidazoles, when K_2CO_3 was replaced by t-$BuNH_2$, which avoids side reactions of TosMIC (see below). Instead of t-$BuNH_2$ other amines may be used also, specifically those from which the aldimines (**2**) are derived (see **3j** and **3k**). This is of advantage when exchange of amines in **2** becomes a competing reaction.[8]

Synthesis of 1,4,5-Trisubstituted Imidazoles. Monosubstituted TosMIC derivatives of type $TosCHR^3N{=}C$ (**6**, R^3 = aryl or alkyl[9]) also are capable of reacting with aldimines. The trisubstituted imidazoles **7** thus obtained are collected in Table II. Conceivably, the anion of α-tosylbenzyl isocyanide (**6a**, R^3 = Ph) is less nucleophilic than TosMIC anion. This appears from the failure of **6a** to react with N-benzylideneaniline to give **7c** (compare **3e**, Table I). Besides, we have found no indications that **6a** is undergoing a cyclodimerization similar to TosMIC (cf. Scheme II).

Remarkably, both **6a** and α-tosylethyl isocyanide (**6b**, R^3 = Me) give only imidazoles (**7d,e**) under conditions (NaH/DME) that would lead to 2-imidazolines in case of TosMIC.

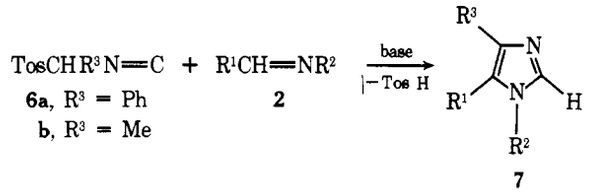
Another type of 1,4,5-trisubstituted imidazoles **11** (Table III) is obtained from TosMIC and imidoyl chlorides[11] (**9**). The chlorine in **9**, which is readily displaced by a variety of nucleophiles,[12] reacts accordingly with TosMIC anion (**8**) to **10** which cyclizes to **11**.[13] The reactivity of **9** requires the use of a nonnucleophilic base in an aprotic solvent. The reaction is carried out simply by adding a mixture of TosMIC and **9** dissolved in DME (or THF) to a stirred suspension of NaH in dry Me_2SO at room temperature.

The synthesis of the tosylimidazoles **11** was successfully carried out with diaryl- and arylalkylimidoyl chlorides, which are relatively stable towards hydrolysis as compared with *dialkyl*imidoyl chlorides.[11] Even the hydrolytically most stable representative of the latter category, i.e., N-cyclohexyl-α,α-dimethylproprionimidoyl chloride (**9**, R^1 = t-Bu; R^2 = c-hex),[11] was found to hydrolyze completely before reaction occurred with TosMIC anion (**8**), presumably by traces of water present in the "dry" Me_2SO.[14]

Base-Induced Decomposition of TosMIC. The results collected in Table I are influenced by the fact that TosMIC itself is not fully stable to certain bases. For example, the half-life of TosMIC [7 mM in MeOH–DME (2:1)] is 40 min when stirred with 2 molar equiv of solid K_2CO_3 at room temperature, in the absence of a substrate. Likewise, the half-life in DME solution with 1 equiv of NaH is roughly 15 min. On the other hand, TosMIC is fully stable for at least 65 h in MeOH or DME with 0.5–20 equiv of t-$BuNH_2$.

From the fairly complex reaction mixture obtained from

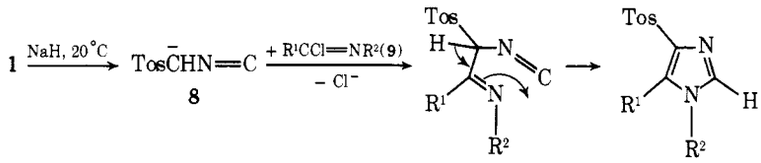
Table II. 1,4,5-Trisubstituted Imidazoles (7) from Monosubstituted TosMIC Derivatives (6) and Aldimines (2)



Compd	R^1	R^2	R^3	Base/solvent	Temp, °C	Time, h	Yield, %	Mp, °C
7a	CH_3	$(CH_3)_3C$	C_6H_5	t-$BuNH_2$/DME	20	0.5	89	74–75 Bp 140 (0.02 mm)
7b	C_6H_5	CH_3	C_6H_5	K_2CO_3/MeOH	20	16	90	156–158 (lit.[10] 158)
7c	C_6H_5	C_6H_5	C_6H_5	t-$BuNH_2$/DME	20	16	*a*	
7c	C_6H_5	C_6H_5	C_6H_5	K_2CO_3/MeOH–DME	20	16	*b*	
7c	C_6H_5	C_6H_5	C_6H_5	NaH/DME	25	1	*c*	
7d	C_6H_5	p-$O_2NC_6H_4$	C_6H_5	NaH/DME	−5	1	82	227–228
7e	C_6H_5	p-$O_2NC_6H_4$	CH_3	NaH/DME	0	1	75	201–203

[a] 74% of 6 recovered; no 7c detected (not even after 2 h of reflux). [b] No 7c obtained; 6 and 2 still present according to TlC. [c] 80% of 6 recovered.

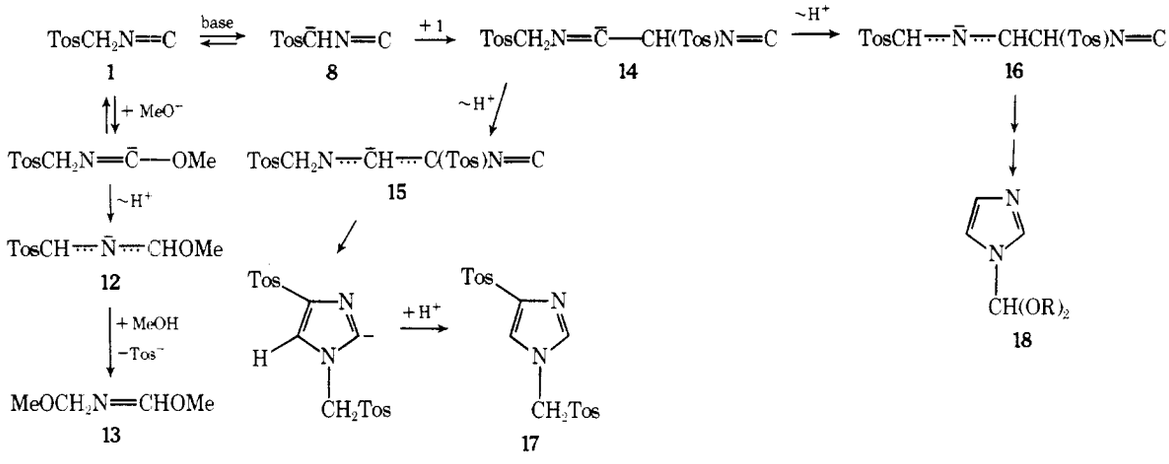
Table III. 4-Tosylimidazoles (11) from Imidoyl Chlorides (9) and TosMIC (1)



Compd	R^1	R^2	Solvent	Time, h	Yield, %	Mp, °C
11a	C_6H_5	C_6H_5	DME–Me_2SO	1	60	188–189
11b	C_6H_5	p-$O_2NC_6H_4$	DME–Me_2SO	1	81	231–232
11c	p-$O_2NC_6H_4$	C_6H_5	DME–Me_2SO	1	85	240–240.5
11d	C_6H_5	c-C_6H_{11}	THF–Me_2SO	1	80	215–216
11e	p-$O_2NC_6H_4$	c-C_6H_{11}	THF–Me_2SO	1	75	264–265
11f	$(CH_3)_3C$	c-C_6H_{11}	THF–Me_2SO		*a*	

[a] Both in THF–Me_2SO as well as THF–HMPA, 9 was hydrolyzed quantitatively to N-cyclohexyl-α,α-dimethylpropionamide.

Scheme II. Decomposition Products of TosMIC Formed under Basic Conditions



TosMIC with K_2CO_3 in MeOH, we could isolate three compounds: **13**, **17**, and **18** (R = Me) in 4, 2, and 20% yields, respectively (Scheme II; for structural evidence see Experimental Section). When a similar decomposition of TosMIC was carried out with 1 equiv of TlOEt in DME–EtOH (2.5:1), imidazole **17** was obtained as the main product (45%), together with 32% of **18** (R = Et). Obviously, the imidazoles **17** and **18** result from a cyclodimerization of TosMIC.

We tentatively explain the formation of **13** by nucleophilic attack of MeO^- on the isocyano carbon[15] of TosMIC, followed by a proton shift to give **12** and an addition–elimination reaction as indicated. A similar nucleophilic attack of TosMIC anion (**8**) on a second molecule of TosMIC would lead to **14**, which can undergo two different proton shifts to the azaallyl anions **15** and **16**, respectively. Ring closure of **15** by nucleophilic attack of the negative nitrogen at the isocyano carbon would give **17**. A combination of steps of unknown sequence, comparable to **12** → **13** and **15** → **17**, and including elimination of TosH, would form **18** from intermediate **16**.

In any event, the structures of **17** and **18** refute the recently

proposed substitution of the tosyl group in TosMIC by TosMIC anion (8).[16]

4-Tosyl-2-imidazolines (4). Structure and H–D Exchange. NaH-induced addition of TosMIC to diarylaldimines in DME leads to 4-tosyl-2-imidazolines (**4b,d,e,f,** Scheme I), which are intermediates in the synthesis of the imidazoles **3** (Table I). Only one stereoisomer is formed (**4b,e,f,** according to ^1H and ^{13}C NMR, and sharp melting point), to which we have assigned the trans configuration on the basis of a detailed spectral analysis of **4b.**

The regioisomeric alternative for **4b,** i.e., 1-*p*-nitrophenyl-5-phenyl-2-tosyl-3-imidazoline (**5b**), was excluded by H–D exchange experiments. Elimination of TosH from either **4b** or **5b** would lead to the same imidazole **3b.** However, H–D exchange in **5b** at 2-C prior to elimination of TosH should lead to **3b** (2-CD), whereas **4b** similarly should give **3b** (4-CD). In fact, **3b** when formed with K_2CO_3 in CD_3OD (reaction C) contained 100% 4-CD and 40% 2-CD. Under the conditions of our reaction, incorporation of deuterium in **3b** (i.e., after elimination of TosH) was found to take place only at 2-C, not at 4-C.[17] Therefore, the quantitative incorporation of 4-CD in **3b** must occur before elimination of TosH and, thus, the initially formed cycloadduct has structure **4b.** Indeed, the ^1H NMR of **4b** in CD_3OD–$CDCl_3$ (1:2) run 5 min after the addition of some solid K_2CO_3 showed that the 4-CH was completely exchanged for 4-CD.[18]

The 100-MHz ^1H NMR spectrum of **4b** shows a one-proton doublet of doublets at δ 5.14 (J = 5 and 1.5 Hz) for 4-CH and a one-proton doublet at δ 5.85 (J = 5 Hz) for 5-CH, indicating a trans J_{4H-5H} of 5 Hz.[19] Furthermore, a 33% NOE enhancement is obtained for both the 4-CH and 5-CH signals upon irradiation of the C_6H_5 peak (at δ 7.36). This also is consistent with trans **4b,** although there is, unfortunately, a complicating factor in that the protons ortho to the tolyl methyl (at δ 7.33 and 7.42) were irradiated simultaneously with the C_6H_5 protons.[20]

Discussion

A mechanistic rationale for the reaction of TosMIC and analogues with aldimines is given in Scheme III. The reaction of TosMIC anion (**8,** R^3 = H) is depicted as a two-step anionic 1,3-dipolar cycloaddition.[21] A concerted process[22] has not been ruled out, however.

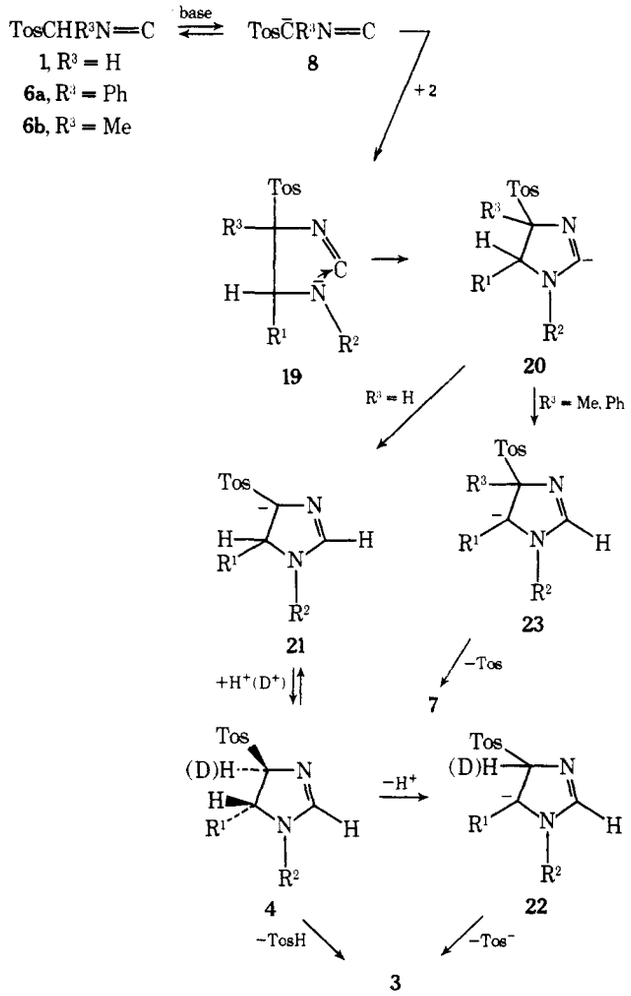
The assumption of nucleophilic attack of **8** through its α carbon is consistent with the results of both classical and phase-transfer alkylations of TosMIC, which lead to α-alkyl TosMIC derivatives,[9,23a] such as **6b.**

Intramolecular nucleophilic attack of the negative nitrogen in **19** on the carbenelike isonitrile carbon[24] will lead to **20.** When R^3 = H, **20** will tautomerize to **21,** since the 4-CH of **4** is the most acidic proton as was shown by H–D exchange experiments (see above).

When the reaction is carried out with NaH in DME, **21**-Na^+ will be the final stage. By workup with water **4** precipitates in the thermodynamically most favorable trans configuration as was shown specifically for **4b.** When, on the other hand, the reaction is carried out in protic medium (K_2CO_3 in MeOH), **4** has the possibility to eliminate TosH to give **3.** It is not known whether this occurs as a cis elimination from **4,** as a trans elimination from the cis isomer of **4,** or through **22** (E1cB mechanism). Direct conversion of **20** to **22** seems unlikely, however, in view of the H–D exchange results obtained with **4b.**

Another argument against the direct conversion **20** → **22** is derived from the following: TosMIC reacts, for instance, with *N*-benzylidene-*p*-nitroaniline without loss of TosH to the 2-imidazoline **4b** (73% yield) when NaH is used in DME. In the corresponding reaction of the monosubstituted TosMIC

Scheme III. Rationale for the Formation of 2-Imidazolines (4) and Imidazoles (3 and 7) from Aldimines (2) using TosMIC (1) and Analogues (6)[a]



[a] Cf. Scheme I and Tables I and II.

derivatives **6a** and **6b,** however, imidazoles are formed directly [Table II, **7d** (82%) and **7e** (75%), respectively]. To solve this seeming inconsistency, it should be realized that for R^3 = Ph or Me the conversion **20** → **21** (Scheme III) is blocked. Now, **20** will tautomerize to **23** (which is the equivalent of **22** for $R^3 \neq$ H), and lose Tos^- to give **7.**

Under those conditions where **1** and **8** can exist together, the cyclodimerization of TosMIC (described above, Scheme II) can become a serious problem. This may be the case when (1) the substrate is not reactive enough toward **8,** and (2) the equilibrium **1** ⇄ **8** is not shifted sufficiently to the right. Presumably, pertinent examples are at hand in the synthesis of **3e** and **3h,** where K_2CO_3/MeOH was used in combination with relatively unreactive aldimines.

One way to circumvent the problem of cyclodimerization of TosMIC is to replace K_2CO_3 by *t*-$BuNH_2$ (or other primary amines, as with **3j** and **3k**). As was indicated above, TosMIC is stable in MeOH (or DME) in the presence of *t*-$BuNH_2$. Apparently, no cyclodimerization is taking place under these conditions. We tentatively ascribe this to decreased nucleophilicity of a $TosC^-HN{=}C/t\text{-}BuN^+H_3$ complex of some sort, which no longer reacts with TosMIC, but which does give imidazoles with the more reactive aldimines, i.e., the dialkylaldimines. The differences in the results obtained with **3h** and with **3i** using *t*-$BuNH_2$ instead of K_2CO_3 may reflect this view. Unfortunately, diaryl- and arylalkylaldimines are not reactive enough, apparently, to give imidazoles under these conditions (see **3c** and **3n**).

Experimental Section

General. The routine ^1H NMR spectra were recorded on a Varian A-60 or A-60D apparatus in δ (ppm) downfield from internal Me_4Si. The 100-MHz ^1H and 25-MHz ^{13}C spectra were taken on a Varian XL100-15 (FT). The mass spectra (70 eV) were recorded on a AEI MS-902 instrument by Mr. A. Kiewiet. Melting points were determined on a Mettler FP1 apparatus equipped with a Mettler FP52 microscopic attachment. Elemental microanalyses were carried out in the Analytical Department of our laboratory.

Solvents were distilled prior to use: DME and THF from $LiAlH_4$, MeOH from Mg. Anhydrous Me_2SO was stored over sieves. The compounds **3h–k, 4b,d–f, 7d,e,** and **11a–e** were prepared under nitrogen. The 55% dispersion of NaH in mineral oil was used as such, or previously washed free of oil (**11a–f**).

Tosylmethyl Isocyanide (TosMIC, 1).[23,25] The synthesis of the precursor *N*-(tosylmethyl)formamide[26] should be carried out with excess of formamide. A stirred mixture of sodium *p*-toluenesulfinate (267 g, 1.5 mol), 750 ml of water, 35% formaldehyde in water (350 ml, 378 g, ca. 4.4 mol), formamide (600 ml, 680 g, 15 mol), and formic acid (244 g, 5.3 mol) was heated at 90 °C for 2 h. The mixture was cooled to room temperature and then in ice–salt with continued stirring, and next cooled overnight at −20 °C. The white solid was washed thoroughly with water, and dried via dissolving in CH_2Cl_2 ($MgSO_4$). The crude product (134–150 g, 42–47%, mp 106–110 °C; mp of pure compound 108–110 °C) was used without purification in the next step.

A stirred suspension of crude *N*-tosylmethylformamide (107 g, 0.50 mol), 250 ml of DME, 100 ml of dry Et_2O, and 350 ml (255 g, 2.5 mol) of Et_3N was cooled in ice–salt to −5 °C. A solution of $POCl_3$ (50 ml, 84 g, 0.55 mol) in 60 ml of DME was added dropwise, while keeping the temperature between −5 and 0 °C (about 1 h). The suspension should turn brown near the end of the addition. After stirring for 30 min at 0 °C, 1.5 l. of ice–water was added with continued stirring. The fine, brown, crystalline solid was collected after stirring for another 30 min and washed with cold water. For purification the wet product was dissolved in benzene (400 ml, 40 °C), the water layer was removed, and the benzene layer was dried ($MgSO_4$). The benzene solution was treated with activated carbon (**2g**) for 5 min at 60 °C. Addition with swirling of petroleum ether (1 l., bp 40–60 °C) provides 74–82 g of light-brown **1** (76–84%, mp 111–114 °C slight dec). This material can be used without further purification. Completely colorless **1** was obtained by rapid chromatography over alumina (CH_2Cl_2), followed by crystallization from MeOH: mp 116–117 °C; IR (Nujol) 2150 (N&v2C), 1320 and 1155 cm^{-1} (SO_2); ^1H NMR δ 4.59 (s, 2, CH_2).

α-Tosylbenzyl Isocyanide (6a).[3c,23a] *n*-BuLi (100 ml, 20% in hexane, 0.22 mol) was added dropwise in 0.5 h to benzyl isocyanide[27] (11.7 g, 0.10 mol) in 180 ml of THF at −65 °C. After stirring for 5 min, a solution of tosyl fluoride (17.4 g, 0.10 mol) in 60 ml of THF was added dropwise keeping the temperature at −60 °C (about 0.5 h). After stirring for another 5 min without cooling the mixture was poured in 1.2 l. of water. The water layer was neutralized (HCl) and extracted with benzene (2 × 200 ml). The benzene extract was dried ($MgSO_4$) and concentrated to give a pale yellow solid, which was washed with CCl_4 providing 22.2 g (82%) of **6a,** mp 128–130 °C dec, reported[23a] previously 124–125 °C.

Alternatively, **6a** can be prepared by the dehydration method used for TosMIC. To a stirred suspension of crude *N*-(α-tosylbenzyl)formamide (2.9 g, 10 mmol, see below) in 20 ml of DME was added in 5 min at −10 °C 2.2 ml (3.7 g, 24 mmol) of $POCl_3$ and, next, in 10 min a solution of Et_3N (7.0 ml, 5.5 g, 50 mmol) in 5 ml of DME. The mixture was stirred for 90 min at −5 °C, then poured in 100 ml of saturated $NaHCO_3$ solution. The resulting brown, crystalline solid was collected and washed with water. The wet product was dissolved in 15 ml of CH_2Cl_2, the water was removed, and the organic layer was dried ($MgSO_4$). Removal of the solvent gave 2.3 g (85%) of crude brown **6a,** mp 115–125 °C dec. After one recrystallization from MeOH, 1.63 g (60%) of **6a** was obtained, mp 128–129 °C dec.

***N*-(α-Tosylbenzyl)formamide.** The procedure of Olijnsma et al.[26] was improved. A stirred mixture of sodium *p*-toluenesulfinate (107 g, 0.60 mol), water (300 ml), benzaldehyde (62 ml, 64 g, 0.90 mol), formamide (240 ml, 271 g, 6 mol), and formic acid (80 ml, 98 g, 2.1 mol) was heated at 60 °C for 6 h. The mixture was cooled to room temperature with continued stirring, and the precipitate was collected and washed thoroughly with water (50 ml) and Et_2O (6 × 50 ml), providing 78 g (45%) of white *N*-(α-tosylbenzyl)formamide, mp 165–166 °C. The combined mother liquor and the concentrated Et_2O washings were heated for another 46 h at 60 °C to give a second crop of product (70 g, 39%, mp 160–162 °C). Both fractions, in total 148 g (84%, reported[26] 15%, mp 160–161 °C), can be used without further purification.

5-*p*-Nitrophenyl-1-phenylimidazole (3a). A solution of TosMIC (975 mg, 5.0 mmol) and *N*-*p*-nitrobenzylideneaniline[28] (678 mg, 3.0 mmol) in a mixture of 20 ml of MeOH and 10 ml of DME was stirred with solid K_2CO_3 (828 mg, 6.0 mmol) for 16 h at room temperature. The solvent was removed under vacuum. The residue was digested with 25 ml of saturated NaCl solution to give a yellow precipitate, which was collected by suction filtration, dissolved in 25 ml of CH_2Cl_2, and drie ($MgSO_4$). The solvent was removed under vacuum and the solid residue was washed twice with Et_2O to provide 650 mg (82%) of light yellow **3a,** mp 162–165 °C. Recrystallization from EtOH (twice) gave an analytically pure sample: mp 164–165 °C; IR (Nujol) 1520 and 1340 (NO_2), 3100 (2-CH), 1590 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 7.15–8.25 (m, C_6H_5, *p*-$NO_2C_6H_4$, 2-CH and 4-CH).[29] Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.93; H, 4.18; N, 15.84. Found: C, 67.8; H, 4.2; N, 15.9.

1-*p*-Nitrophenyl-5-phenylimidazole (3b, Method A). A solution of TosMIC (293 mg, 1.5 mmol) and *N*-benzylidene-*p*-nitroaniline[30] (226 mg, 1.0 mmol) in a mixture of 7 ml of MeOH and 3 ml of DME was stirred with K_2CO_3 (276 mg, 2.0 mmol) at reflux for 1 h. Workup as for **3a** provided **3b** as a yellow solid (187 mg, 70%), mp 149–152 °C, which was recrystallized twice from MeOH to give an analytically pure sample: mp 154–155 °C; IR (Nujol) 3140 (2-CH), 1520 and 1350 cm^{-1} (NO_2); 100-MHz ^1H NMR ($CDCl_3$) δ 8.20 and 8.28 (lower half of AB q, $O_2NC_6H_4$), 7.82 (br s, 1, 2-CH), 7.0–7.5 (m, 8, C_6H_5 + 4-CH^+, other half AB q of $O_2NC_6H_4$);[29] ^{13}C NMR ($CDCl_3$) δ 141.3, 124.5, 125.2, and 146.3 (4-$O_2NC_6H_4$, carbons 1, 2, 3, and 4, respectively), 128.3, 127.9, 128.3, and 127.6 (C_6H_5, carbons 1, 2, 3, and 4, respectively) (aryl assignments are tentative), 138.1 (2-C, $^1J_{2C-H}$ = 211, $^3J_{2C-H}$ = 11.5 Hz), 132.2 (5-C), 129.5 (4-C, $^1J_{4C-H}$ = 190, $^3J_{4C-H}$ = 10.5 Hz);[31] mass spectrum *m/e* (rel abundance) M^+ 265 (100), 266 (20). Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.93; H, 4.18; N, 15.84. Found: C, 67.7; H, 4.2; N, 15.9.

3b (2-CD). H–D exchange[17] was effected by refluxing **3b** (120 mg, 0.45 mmol) and K_2CO_3 (80 mg, 0.57 mmol) in 2 ml of CD_3OD. According to mass spectral analysis only one H, i.e., 2-CH at δ 7.8, was exchanged after 6 h of reflux [h of reflux, *m/e* (rel abundance)]: 1, 265 (100), 266 (100), 267 (21); 3, 265 (26), 266 (100), 267 (30); 6, 265 (10), 266 (100), 267 (26). ^{13}C NMR ($CDCl_3$): compared to **3b** (all H) the 2-C peak at δ 138.1 is reduced from a pair of doublets to a doublet with J = 211 Hz, and the 4-CD signal at 129.5 shows (enlarged spectrum) a very weak triplet of broad lines, J = ca. 30 Hz.

3b, Method B + C. A stirred suspension of imidazoline **4b** (see below, 0.33 g, 0.78 mmol) and solid K_2CO_3 (0.22 g, 1.56 mmol) in 8 ml of MeOH was refluxed for 0.5 h. After removal of the solvent and addition of water, the aqueous layer was extracted with CH_2Cl_2. After drying ($MgSO_4$) and removal of the solvent an oily residue was obtained, which solidified after treating with ether–petroleum ether (bp 40–60 °C, 1:1), yielding 186 mg (90%) of **3b,** mp 152–155 °C.

The same reaction carried out in CD_3OD provided deuterated **3b,** mp 153–155 °C, in 84% yield. This product contained 100% 4-CD and 40% 2-CD, mass spectrum *m/e* (rel abundance) 265 (13), 266 (96), 267 (100), 268 (22).

1-*p*-Nitrophenyl-5-phenyl-4-tosyl-2-imidazoline (4b). To a stirred suspension of 5.0 g (0.12 mol) of NaH (ca. 55% in mineral oil) in 50 ml of DME at −20 °C under N_2 was added in 0.5 h a mixture of *N*-benzylidene-*p*-nitroaniline[30] (11.3 g, 50 mmol) and TosMIC (10.8 g, 55 mmol) dissolved in 250 ml of DME. The temperature was kept at −20 °C. After stirring for an additional 15 min, 750 ml of cold water was added. The resulting yellow precipitate was collected, washed with water, ether, and petroleum ether, and then dissolved in CH_2Cl_2 (700 ml), dried ($MgSO_4$), and treated with activated carbon (1 g). After concentration to about 400 ml, Et_2O was added to turbidity followed by cooling, finally at −20 °C, providing 15.4 g (73%) of **4b,** mp 173–174 °C. After two recrystallizations (CH_2Cl_2) analytically pure material was obtained: mp 174–175 °C; IR (Nujol) 1310 and 1145 (SO_2), 1510 and 1330 cm^{-1} (NO_2); 100-MHz ^1H NMR ($CDCl_3$) δ 2.43 (s, 3, CH_3), 6.96, 7.05, 8.06, 8.16 (AB q, $O_2NC_6H_4N$, J = 9.2 Hz), 7.33, 7.42, 7.84, 7.92 (AB q, $CH_3C_6H_4SO_2$, J = 8.4 Hz), 514 (d of d, 1, 4-CH, J = 5 and 1.5 Hz), 5.85 (d, 1, 5-CH, J = 5 Hz), 8.07 (d, 1, 2-CH, J = 1.5 Hz), the doublet character of the 2-CH signal, as well as the assignment of the two AB q was confirmed by INDOR; ^{13}C NMR ($CDCl_3$, proton decoupled, assignment tentative) δ 152.6 (a), 145.5 (b), 142.6 + 142.4 (c), 137.2 (2-C), 132.9 + 129.8 + 129.6 + 129.3 + 129.1 + 128.8 (e), 125.6 + 125.4 (f), 114.3 (g), 94.6 (5-C), 61.6 (4-C), 21.5 (CH_3) (4-$O_2NC_6H_4$, a, g, f, c, respectively; 4-$CH_3C_6H_4SO_2$, b, e, e, d, respectively; C_6H_5, c, e, e, f, respectively). Anal. Calcd for $C_{22}H_{19}N_3O_4S$: C, 62.69; H, 4.55; N, 9.97; S, 7.61. Found: C, 62.3; H, 4.6; N, 10.0; S, 7.4.

NOE measurements were performed in a degassed CD_2Cl_2 solution; see text.

H–D exchange was carried out in a NMR tube by adding solid K_2CO_3 to a solution of **4b** in CD_3OD–$CDCl_3$ (1:2); the results are discussed in the text.

1-*tert*-Butyl-5-methyl-4-phenylimidazole (7a). To a stirred solution of α-tosylbenzyl isocyanide (**6a**, 542 mg, 2.0 mmol) and *N*-ethylidene-*tert*-butylamine[32] (300 mg, 3.0 mmol) in 10 ml of DME was added in 10 min a solution of *t*-$BuNH_2$ (212 mg, 3.0 mmol) in 5 ml of DME. After 0.5 h the mixture was filtered, the solvent was removed, and the residue was distilled, providing **7a** as a pale yellow oil (380 mg, 89%): bp 140 °C (0.02 mm); ^1H NMR (CCl_4) δ 1.61 (s, 9, *tert*-butyl), 2.47 (s, 3, 5-CH_3), 6.9–7.6 (m, 6, 2-CH and 4-C_6H_5). The yellow oil solidified, but was not purified by crystallization, owing to its high solubility in the common organic solvents. An analytically pure sample was obtained after repeated distillation, mp 74–75 °C. Anal. Calcd for $C_{14}H_{18}N_2$: C, 78,47; H, 8.46; N, 13.07. Found: C, 78.4; H, 8.6; N, 13.0.

4-Methyl-5-phenyl-1-*p*-nitrophenylimidazole (7e). This experiment was carried out by Dr. O. Possel according to **4e** with α-tosylethyl isocyanide[9] (1.50 g, 7.3 mmol), *N*-benzylidene-*p*-nitroaniline[30] (1.63 g, 7.3 mmol), and NaH (240 mg, 10 mmol) at 0 °C. The CH_2Cl_2 solution was evaporated and the solid residue (2.3 g) was crystallized from EtOH to give 1.4 g (75%) of yellow **7e**: mp 201–203 °C; IR (Nujol) 3120 (2C–H), 1335 and 1515 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 2.33 (s, 3, CH_3), 7.0–7.6 (m, 7, C_6H_5 + $O_2NC_6H_4$, upper half AB q), 7.81 (s, 1, 2-CH), 8.19 and 8.35 (d, 2, lower half $O_2NC_6H_4$ AB q); mass spectrum M^+ *m/e* 279. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.8; H, 4.7; N, 15.0.

1,5-Diphenyl-4-tosylimidazole (11a). A solution of TosMIC (390 mg, 2.0 mmol) and *N*-phenylbenzimidoyl chloride[11] (426 mg, 2.0 mmol) in 5 ml of DME was added in 15 min to a suspension of NaH (50 mg, 2.0 mmol) in 5 m of DME at room temperature under N_2. The reaction mixture was stirred for 45 min and, next, slowly poured in water. The precipitate was collected and crystallized from benzene–petroleum ether (bp 40–60 °C, 1:1), providing **11a** as a white solid (450 mg, 60%), mp 186–187 °C. An analytically pure sample was obtained after one further crystallization from benzene–petroleum ether (1:1): mp 188–189 °C; IR (Nujol) 3120 (2C–H), 1320 and 1155 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.82 (d, 2, lower half of C_6H_4), 6.8–7.4 (m, 13, 1- and 5-C_6H_5, 2-CH, and upper half of C_6H_4), 2.4 (s, 3, *p*-CH_3). Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48; S, 8.56. Found: C, 70.47; H, 4.85; N, 7.42; S, 8.48.

Base-Induced Decomposition of TosMIC. With K_2CO_3. TosMIC (9.75 g, 50 mmol) and K_2CO_3 (13.8 g, 100 mmol) were stirred in 75 ml of absolute MeOH at room temperature for 20 h. No more TosMIC was present according to TLC. The solvent was removed, water was added, and the water layer was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated to give 1.47 g of a yellow oil that was subjected to a Kugelrohr distillation at 0.1 mm. Thus were obtained (1) 0.94 g of distillate consisting of about 70% (5 mmol, 20%) of 1-(dimethoxymethyl)imidazole (**18**, R = Me) by ^1H NMR comparison with an independently synthesized sample (see below), and conversion to the picrate of unsubstituted imidazole (formed in situ by hydrolysis) in 60% yield; (2) in the cold trap 200 mg (ca. 4%) of an oil which we assume to be methyl *N*-(methoxymethyl)-formimidate (**13**) [IR (neat) 1670 cm^{-1} (C=N); ^1H NMR (CCl_4) δ 3.48 (s, 3, CH_3OCH_2), 3.65 (s, 3, CH_3OCH=), 4.59 (d, 2, J = 1 Hz, CH_2), and 7.58 (s, 1, CH=N); ^{13}C NMR δ 155.2 (CH=N, $^1J_{C-H}$ = 195 Hz), 83.9 (CH_2, $^1J_{C-H}$ = 150 Hz), 55.6 (CH_3OCH_2, $^1J_{C-H}$ = 142 Hz), 52.6 (CH_3OCH=, $^1J_{C-H}$ = 147 Hz) (long-range C–H coupling constants not determined)]; (3) the distillation residue (0.27 g) which was chromatographed over alumina (CH_2Cl_2) to give 0.20 g (2%) of 4-tosyl-1-(tosylmethyl)imidazole (**17**) [mp 179–180 °C (after crystallization from MeOH); IR (Nujol) 3215 and 3145 (5C–H and 2C–H), 1135–1175 and 1310–1340 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.41 (s, 6, two CH_3), 5.11 (s, 2, CH_2), 7.0–7.9 (m, 10, two C_6H_4 + 2-CH and 5-CH); ^{13}C NMR δ 140.5 (2-CH, $^1J_{C-H}$ = 216 Hz), 124.9 (5-CH, $^1J_{C-H}$ = 201 Hz); mass spectrum M^+ *m/e* 390]. Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.36; H, 4.65; N, 7.17; S, 16.42. Found: C, 55.3; H, 4.7; N, 7.2; S, 16.3.

With TlOEt. Similarly, from TosMIC (4.0 g, 20.5 mmol) and TlOEt (5.0 g, 20 mmol) in 50 ml of DME and 20 ml of absolute EtOH were obtained, after 24 h at 50 °C, 1.76 g (45%, from MeOH) of **17**, mp 179–180 °C, and 1.0 g (32%) of **18** (R = Et): ^1H NMR ($CDCl_3$) δ 1.21 (t, 6, J = 7 Hz, CH_2CH_3), 3.57 (q, 4, J = 7 Hz, CH_2CH_3), 6.06 [s, 1, $(EtO)_2CH$], 7.06 (m, 2, 4- and 5-CH), 7.71 (broad s, 1, 2-CH).

1-(Dimethoxymethyl)imidazole (18, R = Me) was prepared[33] by slowly distilling MeOH from a mixture of imidazole (6.8 g, 0.10 mol), $(MeO)_3CH$ (21 g, 0.2 mol), and 0.5 g of HCOOH heated for 8 h in an oil bath at 100 °C. Distillation gave 10 g of crude product, bp 62–68 °C (0.2 mm), of which 1 g was chromatographed (alumina, CH_2Cl_2) to give 800 mg (56%) of **18** (R = Me): bp 70 °C (0.1 mm); IR (neat) 3120 cm^{-1} (C=N); ^1H NMR (CCl_4) δ 3.32 (s, 6, CH_3O), 5.98 [s, 1, $(MeO)_2CH$], 6.95 and 6.99 (broad d, 2, 4- and 5-CH), and 7.46 (broad s, 1, 2-CH); ^{13}C NMR δ 133.8 (2-CH, $^1J_{C-H}$ = 210, $^3J_{C-H}$ = 10, $^4J_{C-H}$ = 7 Hz), 127.8 (4-CH, $^1J_{C-H}$ = 189, $^2J_{C-H}$ = $^3J_{C-H}$ = 11Hz), 114.9 (5-CH, $^1J_{C-H}$ = 191, $^2J_{C-H}$ = 17 Hz), 101.6 [$CH(OMe)_2$, $^1J_{C-H}$ = 183, $^3J_{C-OMe}$ = 5 Hz], 50.8 (CH_3O, $^1J_{C-H}$ = 144, $^3J_{C-H}$ = 4 Hz). Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.70; H, 7.09; N, 19.71. Found: C, 50.8; H, 7.2; N, 19.50.

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Registry No.—**1**, 36635-61-7; **2a**, 785-80-8; **2b**, 785-81-9; **2c**, 10480-05-4; **2d**, 10480-32-7; **2e**, 538-51-2; **2f**, 2362-77-8; **2g**, 1190-79-0; **2h**, 26029-56-1; **2i**, 7020-80-6; **2j**, 1193-93-7; **2k**, 2875-93-0; **2l**, 622-29-7; **2m**, 17972-13-3; **2n**, 877-80-5; **3a**, 61278-54-4; **3b**, 61278-55-5; **3b** 2-CD, 61278-70-4; **3c**, 61278-56-6; **3d**, 61278-57-7; **3e**, 61278-58-8; **3f**, 61278-59-9; **3g**, 61278-61-3; **3h**, 61278-62-4; **3h** picrate, 61278-63-5; **3i**, 61278-64-6; **3j**, 61278-65-7; **3k**, 61278-66-8; **3k** picrate, 61278-71-5; **3l**, 2154-38-3; **3l** picrate, 61278-69-1; **3m**, 61278-67-9; **3n**, 61278-68-0; **4b**, 61278-72-6; **4d**, 61278-73-7; **4e**, 61278-74-8; **4f**, 61278-75-9; **6a**, 36635-66-2; **6b**, 58379-80-9; **7a**, 61278-76-0; **7b**, 50609-88-6; **7d**, 61278-77-1; **7e**, 61278-78-2; **9a**, 4903-36-0; **9b**, 34918-79-1; **9c**, 5466-94-4; **9d**, 31144-23-7; **9e**, 59389-02-9; **11a**, 37118-25-5; **11b**, 37118-26-6; **11c**, 37118-27-7; **11d**, 37118-28-8; **11e**, 37118-29-9; **13**, 61278-79-3; **17**, 61278-80-6; **18** (R = Et), 61278-81-7; **18** (R = Me), 61278-82-8; sodium *p*-toluenesulfinate, 824-79-3; formamide, 75-12-7; *N*-tosylmethylformamide, 36635-56-0; benzyl isocyanide, 10340-91-7; tosyl fluoride, 455-16-3; *N*-(α-tosylbenzyl)formamide, 37643-54-2; CD_3OD, 811-98-3; imidazole, 288-32-4; $(MeO)_3CH$, 149-73-5.

Supplementary Material Available. Additional experimental details, together with spectral data (mainly IR and ^1H NMR) and the procedures of compounds **3c–n**, **4e,f**, **7b,d**, and **11b–e** (7 pages). Ordering information is given on any current masthead page.

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Synthesis of Heterocycles from Aryl Isothiocyanates and Alkyl Azides

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Benzyl azide reacts with aryl isothiocyanates at 60 °C to produce five types of products (**5–9**). The asymmetric bis adducts of type **6**, formed as major components in the early stage of the reactions, rearrange into the more stable symmetric bis adducts **7** under a variety of conditions. Some derivatives of **6** also undergo partial or complete decomposition into the corresponding benzthiazole **15** upon treatment with Dabco. A precursor of the bis adducts, namely **16**, has been synthesized and shown to react with isothiocyanates at room temperature, giving mainly the asymmetric bis adducts of type **6** (namely **18a** and **18b**). Spectral and mechanistic interpretations are presented.

It is surprising that the behavior of aryl isothiocyanates toward organic azides is unknown, although the chemistry of both classes of compounds has been developed extensively. With inorganic azides, aryl isothiocyanates react to give two types of mono cycloadducts which result from addition of the azide onto the C=S (with HN_3)[1] or C=N bond (with N_3^-, R_3SnN_3, and other organometallic azides).[2]

In a previous article,[3] we have reported that alkyl azides react with arylsulfonyl isothiocyanates at room temperature to give 4-alkyl-5-arylsulfonylimino-1,2,3,4-thiatriazolines (**1**) as the only reaction products. On gentle heating, these adducts decompose into sulfonylcarbodiimides via the intermediacy of iminothiaziridines or their ring-opened dipolar species (**1** → **2** → **3**). Trapping of **2** with many unsaturated compounds (a=b) have led to the synthesis of a large number of other five-membered heterocycles (**4**).[3,4]

Reported here are the results of an extensive investigation on the reactions of aryl isothiocyanates with alkyl azides (in particular benzyl azide), a study complicated by the occurrence of isomerizations during the reaction and also by the number of isomeric reaction products which were difficult to characterize unambiguously by conventional spectroscopic methods (IR, ^{1}H NMR, and MS).[5]

Product Studies. Treatment of benzyl azide with 2 equiv of aryl isothiocyanate at 60 °C led to slow evolution of nitrogen and isolation of five products: a tetrazolinethione **5**, two thiadiazolidines **6** and **8**, and two dithiazolidines **7** and **9**. Since