Base-Induced Cycloaddition of *N*-(Tosylmethyl)imino Compounds to Michael Acceptors. Synthesis of 2,3,4-Trisubstituted Pyrroles

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A series of *N*-(tosylmethyl)imino compounds [$TosCH_2N{=}C(L)A$] has been prepared, and applied to a new, base-induced, one-operational synthesis of otherwise more difficultly accessible 2,3,4-trisubstituted pyrroles from electron deficient olefins. This regiospecific process probably is an 1,3-anionic cycloaddition, combined with the elimination of sulfinic acid and a leaving group L. The group A is retained as the 2-substituent of the resulting pyrroles.

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The combination of a sulfonyl, a methylene and an isocyano group as in tosylmethyl isocyanide (TosMIC, **1**), provides a molecule of diverse and powerful synthetic utility. The applications of **1** are, in part, based on transfer of the $CH_2N{=}C$ moiety to unsaturated substrates, for example Michael acceptors, to form 1,2,5-unsubstituted pyrroles (2). Variations in the methylene and the sulfonyl parts of **1** lead to further extensions of tosylmethyl isocyanide chemistry which have been subject of previous reports (2,3). Now changes at the isocyano side of **1** are under investigation, which includes the preparation and synthetic applications of compounds of type **2** and **3**.

$RSO_2CH_2N{=}C$ **1** (TosMIC)

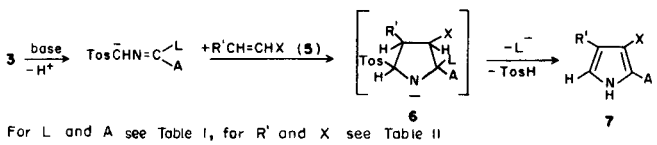
$RSO_2CH_2N{=}C{=}Z$ **2** (Z, reference 4)

$RSO_2CH_2N{=}C(L)A$ **3** (L,A, see text)

(R = p-tolyl)

The conjugate bases (**4**) of **3** react with Michael acceptors as depicted in Scheme I to give trisubstituted pyrroles **7** (Table II) (5). In order to arrive at compounds with an aromatic sextet one of the substitutents (L) in **3** should be a leaving group, while the other (A) is retained in the product **7**. In a related fashion tosylmethyl isocyanide (*i.e.* L and A are void in **4**) leads to disubstituted pyrroles (**7**, A = H), and with different substrates to other azoles as well (2). Recently, we have shown that 2-amino-1,3-oxazoles can be synthesized by a comparable reaction from carbodiimides **2** (Z = NR) and aldehydes (4).

Scheme I



For L and A see Table I, for R' and X see Table II

In reactions of tosylmethyl isocyanide and the derivatives **2** and **3** the tosyl group fulfils the unique role of an activating substituent temporarily present in the carbanion forming phase, which is spontaneously lost by a 1,2-elimination of *p*-toluenesulfinic acid (TosH) in the final stage (2,4). In this respect synthons **3** are an improvement over ester substituted methylimino derivatives, for example $EtOCH_2N{=}C(OEt)R$, which have been used by Cornforth (6) in the synthesis of oxazoles and imidazoles by reaction with ethyl formate in a two step process (*cf.* subsequent paper) (7). Cornforth's reagent lacks the possibility of a direct elimination, comparable to the elimination of *p*-toluenesulfinic acid from **6**, and therefore is much more restricted in the substrates it can react with.

Our new pyrrole synthesis is based on the formation of the C(2)−C(3) and C(4)−C(5) bonds of the ring system, which in itself is not a new approach (8). An attractive aspect of the present method is, however, the possibility of introducing in **7** both carbon substituents or hetero substituents in the 2-position by variation of group A in **3** (Table II). We have employed for A the following groups: Me, Ph, MeS and MeO; for leaving group (L) MeS, MeO and Cl were used (Tables I and II). In a subsequent paper the same synthons **3** are applied to the synthesis of oxazoles and imidazoles (7).

Results and Discussion.

All *N*-(tosylmethyl)imino synthons **3** (Table I) used in this study are new compounds (5). They have been prepared by *S*- or *O*-methylation with methyl fluorosulfonate of the corresponding *N*-(tosylmethyl)(thio)amides (in case of **3a-c**), of methyl *N*-(tosylmethyl)dithiocarbamate (to give **3e**), or by methoxide substitution of chloride in the dichloro adduct of tosylmethyl isocyanide (for **3d** and **3f**). Details are given in the Experimental section (5,9). Compounds **3** are sufficiently stable to be stored without specific precautions, except for **3b**, which can be handled best as a fluorsulfonic salt.

For substrates in the pyrrole syntheses we have selected the following Michael acceptors: α,β-unsaturated ketones, esters and nitriles. The results obtained with these com-

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Table I

N-(Tosylmethyl)imino Compounds $TosCH_2N{=}C\langle^{L}_{A}$ (3)

Compound	L	A	Yield (%)	Mp (°C)
3a	MeS	Ph	74	98.5-100.5
3b	MeO	Me	81	90-93 dec (a)
3c	MeS	Me	73	103-104.5
3d	MeO	MeO	67	108-110
3e	MeS	MeS	93	122-123
3f	Cl	MeO	70	131.5-133

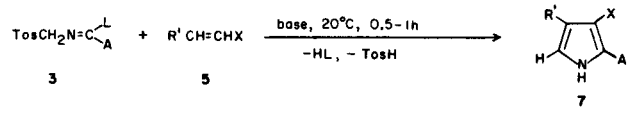
(a) Isolated and used as fluorosulfonate salt.

pounds are collected in Table II. Chalcone (*trans*-phenyl 2-phenylethenyl ketone) is a particularly attractive substrate, which gave positive results with all imines **3** from Table I. In fact, the optimal reaction conditions (base-solvent system) have been determined for each of the individual imino compounds **3** in reactions with chalcone (entries 1,7,8,12,13). We have assumed that these conditions were appropriate for reactions with the other substrates as well.

In addition to entry 1, pyrrole **7a** was formed equally well (in 69% yield) with potassium *t*-butoxide in DME-*t*-butyl alcohol but not with nucleophilic bases like sodium ethoxide or potassium hydroxide. Unlike **3a**, the reaction conditions with **3b** and **3c** were more critical. Good results were obtained with chalcone only in aprotic medium using sodium hydride in DME-DMSO or potassium *t*-butoxide in tetrahydrofuran (entries 7 and 8); much lower yields of **7g** were obtained, however, with butyllithium (in tetrahydrofuran) or with sodio dimethyl sulfoxide (in DME-DMSO). The unsatisfactory results of entries 9 and 10 probably reflect a combination of lower electrophilicity (1,3-anionophilicity) of the substrates as compared with chalcone (10), and the relative instability of the conjugate base of **3c** (and **3b** as well) relative to **3a, d** and **e** (11). Competing formation of a substrate-anion completely prevented reaction to pyrrole **7j** (entry 11), and gave but a low yield of **7f** (entry 6), which reflects the greater stability of the anion derived of **3a**. Synthon **3d** gave 2-methoxypyrrole **7k**, which was air-sensitive like other 2-alkoxypyrroles (12). At-

Table II

Pyrroles **7** Synthesized from *N*-(Tosylmethyl)imino Compounds **3** and Michael Acceptors



Entry	L	A	R'	X	Compound	Yield (%)	Mp (°C)	^{13}C-nmr ($CDCl_3$) δ C(5) (J C(5)-H)
1	MeS	Ph	Ph	PhCO	**7a**	73	198.5-200	117.9 (188.0)
2	MeS	Ph	Ph	MeOOC	**7b**	58	164.5-165.5	
3	MeS	Ph	Ph	C≡N	**7c**	63	266-267	
4	MeS	Ph	Me	MeCO	**7d**	61	165.5-166	
5	MeS	Ph	Me	C≡N	**7e**	39 (a)	141-144.5	
6	MeS	Ph	$EtOOCCH_2$	EtOOC	**7f**	33	121-122	
7	MeO	Me	Ph	PhCO	**7g**	75	235-236 (Lit (14):231)	
8	MeS	Me	Ph	PhCO	**7g**	91	235-236	115.8 (188.0)
9	MeS	Me	Ph	EtOOC	**7h**	10	101-103 (Lit (14):105)	
10	MeS	Me	Ph	C≡N	**7i**	(b)	-	
11	MeS	Me	$EtOOCCH_2$	EtOOC	**7j**	(c)	-	
12	MeO	MeO	Ph	PhCO	**7k**	45 (d)	*ca.* 100 dec	110.0 (188.5)
13	MeS	MeS	Ph	PhCO	**7l**	73	171-173	
14	MeS	MeS	Ph	MeOOC	**7m**	72	110-111.5	119.2 (188.0)
15	MeS	MeS	Ph	C≡N	**7n**	70	183-184.5	
16	MeS	MeS	Me	MeCO	**7o**	41	153.5-155	

(a) Regioisomeric 4-cyano-3-methyl-2-phenylpyrrole was isolated in 3% yield, and was identical with a sample synthesized independently from α-tosylbenzyl isocyanide and crotononitrile, D. van Leusen, unpublished results, *cf.*, reference 8d. (b) No **7i** formed, **5** recovered almost quantitatively. (c) No **7j** formed, with 1.1 equivalent of sodium hydride both reactants recovered. (d) Crude, unstable product.

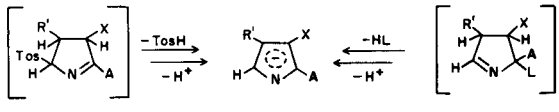
tempts to hydrolyse **7k** to the probably more stable 3-benzoyl-4-phenyl-5*H*-pyrrolin-2-one were unsuccessful (13). Finally, synthon **3e** gave the expected 2-methylthiopyrroles in good yields using excess of potassium *t*-butoxide in DME-*t*-butyl alcohol (entries 13-16). With sodium hydride in DME-DMSO yields were somewhat lower. With one exception only (entry 5) the reactions of Table II were regiospecific.

The structures of the new pyrroles in Table II are established beyond doubt. Two compounds (**7g** and **7h**) have the same melting points reported previously for compounds prepared otherwise. Besides, compounds **7a** and **7g** were identical to the products of a Knorr synthesis (14) obtained in yields of 3 and 73%, respectively. Also, the structure of the regioisomer of **7e** was supported by an independent synthesis (Table II, footnote a). For diagnostic purposes the ^{13}C chemical shifts of the unsubstituted ring carbon C(5) and the ^{1}J C(5)-H values of a series of comparable pyrroles are included in Table II. The coupling constants J of 188.0-188.5 Hz are typical for the α-position. For the parent pyrrole these values are ^{1}J C(2)-H = 182 Hz and ^{1}J C(3)-H = 168 Hz (15). For 4-benzoyl-2-methyl-3-phenylpyrrole, which is a positional isomer of **7g**, the comparable data are δ C(5) = 126.3 and ^{1}J C(5)-H = 188.2 Hz (16), the chemical shift difference with **7g** being due mainly to the influence of the 4-benzoyl substituent (17).

Mechanistic Aspects.

It is reasonable to assume that the first step in our pyrrole synthesis is the formation of anion **4** (Scheme I), which actually is a 2-azaallyl anion (18). This assumption is supported by H-D exchange experiments carried out with **3a** (19). After **4** has been formed, several pathways are conceivable, differing mainly in the sequence of the various elimination processes. A (two-step or one-step) 1,3-anionic cycloaddition (20) of **4** to the substrate molecule (**5**) would give **6** (as is supposed in Scheme I), which *via* **8** (loss of L^-) or **10** (loss of Tos^-) leads to **9**, and eventually on *N*-protonation to **7** (Scheme II). Alternatively, the 1,3-dipoles TosCH-N=$\overset{+}{C}$A$\overset{-}{L}$ (**11**) or HC=N-$\overset{+}{C}$A$\overset{-}{L}$ (**12**) could be formed from **4** by elimination of L^- or Tos^-, respectively. The 1,3-dipolar cycloaddition of **11** or **12** to **5** would again lead to **8** or **10**.

Scheme II



8 9 10

Other things being equal, the isolation of 5-*p*-chlorophenyl-2-phenyl-4-tosyl-2-oxazoline (see subsequent paper (7)) as an intermediate (still containing a tosyl substituent) in the synthesis of 5-*p*-chlorophenyl-2-phenyl-1,3-oxazole from **3a** and *p*-chlorobenzaldehyde may be used, with the help of Occam's Razor, as an argument against a reaction path *via* **12** (→ **10**).

We have sought to differentiate between the remaining routes **4** → **7** *via* **6** or *via* **11**, using compound **3a** (L = MeS, A = Ph), by the following observations: (i) If reaction **4a** → **11a** takes place, it does not appear to be an equilibrium, because in the presence of EtS^- no exchange of MeS in **3a** was observed; (ii) When the reaction of entry 1 (Table II) was carried out without chalcone 64% of **3a** could be recovered after 40 minutes. Thus, irreversible formation of **11a** would allow a maximum yield of 36% of **7a** by this route, whereas 71% is found after 40 minutes. Therefore indications are that a 1,3-anionic cycloaddition is not an unlikely pathway.

EXPERIMENTAL

General.

All experiments, with the exception of those in which water was used as a solvent, were carried out under dry nitrogen. The following solvents were distilled prior to use: DME and THF (from lithium aluminum hydride), dichloromethane and ethyl ether from phosphorus pentoxide, methanol from Mg; anhydrous DMSO and *t*-butyl alcohol were stored over sieves (Linde 4A). Commercial starting compounds were used without further purification, unless otherwise stated. Elemental microanalyses were carried out in the Analytical Department of this laboratory. The following apparatus was used: Varian A-60 (^{1}H-nmr; the aromatic signals of tosyl are approximated by an ABq); Varian XL 100-15 (FT; ^{13}C-nmr); Unicam SP 2000 (ir); AEI MS-902 (70 eV; all new compounds gave satisfactory mass spectra); Reichert with microscopic attachment (mp).

Methyl *N*-(Tosylmethyl)thiobenzimidate (**3a**).

To a solution of *N*-(tosylmethyl)thiobenzamide (see below, 7.63 g, 25 mmoles) in dichloromethane (75 ml) was added methyl fluorosulfonate (3.42 g, 30 mmoles) with a syringe. After stirring for 14 hours the mixture was added to a nearly saturated solution of sodium chloride (150 ml), containing potassium hydroxide (1.96 g, 35 mmoles). After separation, the water layer was extracted twice with dichloromethane. The combined organic layers were dried (magnesium sulfate) and concentrated. The solid residue was crystallized once from a mixture of dichloromethane-ethyl ether-pentane to give 5.90 g (74%) of **3a**, mp 95.5-97°. Recrystallization from the same solvent mixture gave an analytically pure sample, mp 98.5-100.5°; ir (nujol): 1600 C=N, 1320 and 1135 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform; *E-Z* mixture): δ 2.00, 2.34, 2.42 and 2.46 (four s, 6H), 4.68 and 5.04 (two s, 2H), 6.9-8.0 (q + m, 9H, J = 8.5 Hz).

Anal. Calcd. for $C_{16}H_{17}NO_2S_2$: C, 60.16; H, 5.37; N, 4.38; S, 20.07. Found: 60.0; H, 5.4; N, 4.3; S, 19.9.

N-(Tosylmethyl)thiobenzamide.

A solution of *N*-(tosylmethyl)benzamide (14.5 g, 50 mmoles) (21) in DME (150 ml) was stirred for 50 hours with phosphorus pentasulfide (11.1 g, 100 mmoles) after which the excess of phosphorus pentasulfide was removed and the solution concentrated to about 10% of its original volume. The residue was added to a saturated sodium chloride solution (21). The wet precipitate was dissolved in dichloromethane and dried (magnesium sulfate). After removal of the solvent 14.8 g (97%) of product was obtained, mp 142.5-144.5° (lit (22): 140.5-142°). A mixture mp with an authentic sample (22) showed no depression.

Methyl *N*-(Tosylmethyl)acetimidate Fluorosulfonate (**3b**).

Methyl fluorosulfonate (22.8 g, 200 mmoles) was added to a solution of *N*-(tosylmethyl)acetamide (22.7 g, 100 mmoles) (21) in 1,2-dichloroethane

(250 ml) at 55°. After stirring for 3.5 hours at 55° the mixture was cooled to room temperature and pentane (20 ml) was added gradually. Further cooling (to −15°) and addition of more pentane (10 ml) gave 27.5 g (81%) of **3b**, mp 90-93° dec. Methyl *N*-(tosylmethyl)acetimidate (freed from its fluorosulfonate salt by addition to a nearly saturated sodium chloride solution containing 1.5 equivalents of potassium hydroxide followed by extraction with dichloromethane) was characterized spectroscopically without further purification; ir (nujol): 1650 (C=N), 1305 and 1130 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 1.89 (s, 3H), 2.46 (s, 3H), 3.60 (s, 3H), 4.61 (s, 2H), 7.35 and 7.84 (ABq, 4H, J = 8 Hz); ms M^+ m/e 241 (calcd. for $C_{11}H_{15}NO_3S$ 241.3).

Methyl *N*-(Tosylmethyl)thioacetimidate (**3c**).

This compound was prepared analogously to **3a** from *N*-(tosylmethyl)thioacetamide (see below, 13.12 g, 54 mmoles) and methyl fluorosulfonate (6.84 g, 60 mmoles) in a yield of 10.30 g (73%), mp 100-102°. An analytically pure sample was obtained by two crystallizations from a mixture of dichloromethane-ethyl ether-pentane, mp 103-104.5°; ir (nujol): 1610 (C=N), 1310 and 1130 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform; *E-Z* mixture): δ 2.0-2.3 and 2.44 (two s + m, 9H), 4.57-4.76 (s + m, 2H), 7.3 and 7.79 (ABq, 4H, J = 8 Hz).

Anal. Calcd. for $C_{11}H_{15}NO_2S_2$: C, 51.34; H, 5.87; N, 5.44; S, 24.92. Found: C, 51.2; H, 5.9; N, 5.3; S, 24.8.

N-(Tosylmethyl)thioacetamide.

This compound was prepared analogously to *N*-(tosylmethyl)thiobenzamide (see above) from *N*-(tosylmethyl)acetamide (22.7 g, 100 mmoles) (21) and phosphorus pentasulfide (22.2 g, 50 mmoles) in DME (300 ml) for 26 hours to yield 19.8 g (82%) of product, mp 138.5-140.5°. Analytically pure material was obtained by two crystallizations from ethyl ether-pentane mp 142-143°; ir (nujol): 3340 (NH), 1310 and 1130 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.46 (s, 3H), 2.50 (s, 3H), 5.31 (d, 2H, J = 6.5 Hz), 7.31 and 7.79 (ABq, 4H, J = 8.5 Hz).

Anal. Calcd. for $C_{10}H_{13}NO_2S_2$: C, 49.36; H, 5.38; N, 5.75; S, 26.35. Found: C, 49.4; H, 5.2; N, 5.7; S, 26.1.

Dimethyl *N*-(Tosylmethyl)iminocarbonate (**3d**) and Tosylmethyl Isocyanodichloride.

Gaseous chlorine (dried over calcium chloride) was slowly led into a solution of tosylmethyl isocyanide (TosMIC, (23), 13.65 g, 70 mmoles) in dichloromethane (200 ml) at −5° until a sample showed no longer a N=C band at 2150 cm^{-1}. Excess of chlorine was removed with a nitrogen-stream (20 minutes). After careful removal of the solvent crude tosylmethyl isocyanodichloride was dissolved in a solution of sodium (9.66 g, 0.42 mole) in a mixture of methanol (200 ml) and DME (30 ml). [Pure tosylmethyl isocyanodichloride was obtained from dichloromethane-ethyl ether-pentane mp 70-73.5° (lit (24): 70-73.5°)]. The mixture was stirred for 30 minutes at −5°, for 1.5 hours at room temperature, then added to a saturated sodium chloride solution (21). Extraction with ethyl ether, drying (magnesium sulfate), and concentration gave 12.1 g (67%) of **3d**, mp 104.5-107°. An analytically pure sample was obtained by two crystallizations from dichloromethane-ethyl ether-pentane mp 108-110°; ir (nujol): 1660 (C=N), 1310 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.44 (s, 3H), 3.58 (s, 3H) 3.69 (s, 3H), 4.48 (s, 2H), 7.23 and 7.74 (ABq, 4H, J = 9 Hz).

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.87; N, 5.45; S, 12.46. Found: C, 51.4, H, 5.9; N, 5.4; S, 12.5.

Dimethyl *N*-(Tosylmethyl)iminodithiocarbonate (**3e**).

This compound was prepared analogously to **3a** from methyl *N*-(tosylmethyl)dithiocarbamate (see below, 50.0 g, 182 mmoles) and methyl fluorosulfonate (21.8 g, 191 mmoles). Work-up with sodium bicarbonate (21.0 g, 280 mmoles), instead potassium hydroxide, gave 49.1 g (93%) of **3e**, mp 119-121°. Crystallization from dichloromethane-hexane gave an analytically pure sample, mp 122-123°; ir (nujol): 1655 (C=N), 1305 and 1135 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.27 (s, 3H), 2.40 (s, 3H), 2.47 (s, 3H), 4.71 (s, 2H), 7.28 and 7.79 (ABq, 4H, J = 8 Hz).

Anal. Calcd. for $C_{11}H_{15}NO_2S_3$: C, 45.65; H, 5.22; N, 4.84; S, 33.23. Found: C, 45.6; H, 5.3; N, 4.9; S, 33.3.

Methyl *N*-(Tosylmethyl)chloroformimidate (**3f**).

Potassium *t*-butoxide (7.98 g, 70 mmoles) was added portionwise to a solution of crude tosylmethyl isocyanodichloride (prepared as described above, under **3d**, from 9.75 g (50 mmoles) of tosylmethyl isocyanide) in a mixture of methanol (150 ml) and DME (40 ml). After stirring for 30 minutes at −5°, the mixture was added to a saturated sodium chloride solution (21). The precipitate was collected, dissolved in dichloromethane and dried (magnesium sulfate). Concentration and crystallization of the residue from dichloromethane-ethyl ether (1:2) gave 9.20 (70%) of **3f**, mp 130-133°. Two more crystallizations gave an analytically pure sample, mp 131.5-133°; ir (nujol): 1660 (C=N), 1310 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 3.82 (s, 3H), 4.62 (s, 2H), 7.31 and 7.79 (ABq, 4H, J = 8 Hz).

Anal. Calcd. for $C_{10}H_{12}ClNO_3S$: C, 45.89; H, 4.62; Cl, 13.54; N, 5.35; S, 12.26. Found: C, 45.9; H, 4.6; Cl, 13.7; N, 5.3; S, 12.3.

Methyl *N*-(Tosylmethyl)dithiocarbamate.

Prepared according to the procedure for ethyl *N*-(tosylmethyl)dithiocarbamate (25), by stirring a mixture of sodium *p*-toluenesulfinate (35.4 g, 200 mmoles), formaldehyde (33% solution in water, 20 ml, 220 mmoles) and methyl dithiocarbamate (26) in formic acid (100 ml) and water (130 ml) for 16 hours at 35°. On cooling to 0°, the precipitate was collected, washed with water and dried *in vacuo* to give 40.2 g (73%) of product, mp 143-146°. An analytically pure sample was obtained by two crystallizations from methanol, mp 150-152°; ir (nujol): 3330 (NH), 1315 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.46 (s, 3H), 2.57 (s, 3H), 5.33 (d, 2H, J = 6.5 Hz), 7.34 and 7.84 (ABq, 4H, J = 8.5 Hz), 7.7-8.1 (m, 1H).

Anal. Calcd. for $C_{10}H_{13}NO_2S_3$: C, 43.61; H, 4.76; N, 5.07; S, 34.92. Found: C, 43.6; H, 4.8; N, 5.2; S, 35.0.

3-Benzoyl-2,4-diphenylpyrrole (**7a**).

To a stirred suspension of sodium hydride (50% in mineral oil, 0.11 g, *ca.* 2.3 mmoles) in DME (5 ml) and DMSO (1.5 ml) a mixture of **3a** (0.35 g, 1.1 mmoles) and chalcone (0.21 g, 1.0 mmole) was added all at once. Evolution of hydrogen started immediately. After stirring for 1 hour, the reaction mixture was poured in saturated sodium chloride solution (70 ml) and neutralized with 1*N* hydrochloric acid. The yellow precipitate was collected, washed with water and dissolved in dichloromethane. Water was separated, and the organic layer was dried (magnesium sulfate) and concentrated. The residue was crystallized from acetone-ethyl ether-pentane to give 0.24 g (73%) of **7a**, mp 193-195.5°. An analytically pure sample was obtained from acetone-pentane (twice), mp 198.5-200°; ir (nujol): 3250 (NH) and 1625 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 6.91 (d, 1H, J = 2.5 Hz), 7.0-7.7 (m, 14H), 7.7-8.0 (m, 2H).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.43; H, 5.31; N, 4.33. Found: C, 85.3; H, 5.4; N, 4.4.

Isomeric 4-benzoyl-2,3-diphenylpyrrole (27), the expected isomer of **7a** from a non-regiospecific addition of **3a**, was not detectable by tlc in the mother liquor after crystallization of **7a**, *cf.*, however (entry 5, Table II).

Pyrrole **7a** was prepared independently in 3% by a Knorr synthesis (14) from α-aminoacetophenone and dibenzoylmethane. The two preparations were identical (ir and mixture mp).

3-Carbomethoxy-2,4-diphenylpyrrole (**7b**).

Solid imidate **3a** (1.40 g, 4.4 mmoles) was added all at once to a suspension of sodium hydride (50% in mineral oil, 0.58 g, 12 mmoles) in a mixture of DME (18 ml) and DMSO (4 ml). After the evolution of hydrogen had stopped (*ca.* 8 minutes) methyl cinnamate (0.65 g, 4.0 mmoles) was added all at once. After 30 minutes work-up as described for **7a** (washing with 5 ml of ethyl ether-pentane (3:7) gave 0.64 g (58%) of **7b**, mp 158-161°. Analytically pure **7b** was obtained by two crystallizations from dichloromethane-ethyl ether-pentane mp 164.5-165.6°; ir (nujol): 3300 (NH) and 1670 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 3.74 (s, 3H), 6.69 (d, 1H, J = 2.5 Hz), 7.2-7.7 (m, 10H), 8.1-9.0 (m, 1H).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.8;

H, 5.5; N, 5.0.

3-Cyano-2,4-diphenylpyrrole (**7c**).

This compound was prepared analogously to **7b** from **3a** and cinnamonitrile (0.52 g, 4.0 mmoles) and obtained (after washing with ethyl ether) as a solid in a yield of 0.62 g (63%), mp 268-270°. Recrystallization (twice) from acetone gave an analytically pure sample, mp 266-267°; ir (nujol): 3250 (NH) and 2230 cm^{-1} (C≡N); ^{1}H-nmr (DMSO-d_6): δ 7.0-7.9 (m).

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.59; H, 4.95; N, 11.46. Found: C, 83.3; H, 5.0; N, 11.3.

3-Acetyl-4-methyl-2-phenylpyrrole (**7d**).

This compound was prepared analogously to **7b** from **3a** (1.76 g, 5.5 mmoles) and pent-3-en-5-one (90%, 0.47 g, 5.0 mmoles), and worked up as described for **7a**, yielding 0.61 g (61%) of **7d**, mp 164-167°. An analytically pure sample was obtained from dichloromethane, mp 165.5-166°; ir (nujol): 3200 (NH) en 1615 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 2.06 (s, 3H), 2.30 (s, 3H), 6.55 (m, 1H), 7.38 (broad s, 5H), 8.1-9.0 (broad m, 1H).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.37; H, 6.57; N, 7.03. Found: C, 78.3; H, 6.6; N, 7.0.

3-Cyano-4-methyl-2-phenylpyrrole (**7e**) and 4-Cyano-3-methyl-2-phenylpyrrole.

This compound was prepared analogously to **7b** from **3a** (1.40 g, 4.4 mmoles) and crotonitrile (0.27 g, 4.0 mmoles) in 45 minutes, yielding [after two washings with ethyl ether-pentane (3:7)] 0.26 g (36%) of **7e**, mp 141-144°. Concentration of the combined washing liquids, followed by chromatography (preparative tlc on aluminum oxide:benzene) gave a second crop of **7e** (0.021 g, 3%, mp 140-143°) and 0.023 g (3%) of its isomer (4-cyano-3-methyl-2-phenylpyrrole, mp 122-125.5° (rep (27): 126-127°). Three crystallizations from ethyl ether-pentane gave an analytically pure sample of **7e**, mp 141-144.5° (dimorphous); ir (nujol): 3320 (NH) and 2220 cm^{-1} (C≡N); ^{1}H-nmr (deuteriochloroform): δ 2.20 (d, 3H, J = 1 Hz), 6.55 (m, 1H), 7.2-7.7 (m, 5H), 8.5-9.3 (m, 1H).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.37. Found: C, 78.8; H, 5.5; N, 15.3.

3-Carbethoxy-4-carbethoxymethyl-2-phenylpyrrole (**7f**).

This compound was prepared in 45 minutes analogously to **7b** from **3a** (1.60 g, 5.0 mmoles). 1,3-dicarbethoxypropene (1.12 g, 6.0 mmoles) and sodium hydride (*ca.* 8 mmoles), followed by work up as described for **7a** to give a viscous solid, which was washed with ethyl ether-pentane and crystallized from ethyl ether-pentane, yield, 0.50 g (33%) of **7f**, mp 118-121°. An analytically pure sample of **7f** was obtained from ethyl ether-pentane (2 times), mp 121-122°; ir (nujol): 3350 (NH) and 1705, 1690 cm^{-1} (C=O); H-nmr (deuteriochloroform): δ 1.1-1.5 (m, 6H), 3.77 (broad s, 2H), 3.9-4.3 (two q, 4H, J = 7 Hz), 6.45 (broad d, 1H, J = 2.5 Hz), 7.0-7.5 (m, 5H), 8.5-9.3 (m, 1H).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.7; H, 6.3; N, 4.7.

3-Benzoyl-2-methyl-4-phenylpyrrole (**7g**).

Sodium hydride (50% in mineral oil, 0.14 g, *ca.* 3 mmoles) was added to a mixture of **3c** (0.26 g, 1.0 mmole) and chalcone (0.23 g, 1.1 mmoles) in DME (4 ml) and DMSO (1 ml). After 1 hour, work-up as described for **7a**, a white solid was obtained which was washed with water and dried *in vacuo* over phosphorus pentoxide yielding 0.24 g (91%) of **7g**, mp 235-236° slight dec (lit (14): 231°), which was identical with an authentically prepared sample (14); ir (nujol): 3220 (NH) and 1590 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 2.40 (s, 3H), 7.0-7.9 (m, 11H). Pyrrole **7g** was obtained in 75% yield when **3b** was used, instead of **3c**.

3-Carbethoxy-2-methyl-4-phenylpyrrole (**7h**).

Reaction of **3c** (1.29 g, 5.0 mmoles) and ethyl cinnamate (0.81 g, 4.6 mmoles) analogously to **7g** gave a mixture consisting mainly of **7h** and ethyl cinnamate. Column chromatography (aluminum oxide, dichloromethane) gave, after standing for two weeks, 0.15 g of crystalline material, which on recrystallization from ethyl ether-pentane gave 0.10 g (10%) of **7h**, mp 101-103° (lit (14): 105°); ir (nujol): 3350 (NH) and 1660 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 1.21 (t, 3H), 2.50 (s, 3H), 4.23 (q, 2H, J = 7 Hz), 6.50 (d, 1H, J = 2.5 Hz), 7.1-7.5 (m, 5H), 8.2-9.0 (m, 1H).

3-Benzoyl-2-methoxy-4-phenylpyrrole (**7k**).

A solution of **3d** (0.26 g, 1.0 mmole) and chalcone (0.25 g, 1.2 mmoles) in DME (6 ml) was added to a mixture of potassium *t*-butoxide (0.68 g, 6 mmoles) in *t*-butyl alcohol (6 ml). After 1 hour, work-up as described for **7a**, resulted in a viscous solid which was washed with ethyl ether (10 ml) to give 0.12 g (45%) of **7k**, mp *ca.* 100° dec. Further purification was unsuccessful due to instability; ir (nujol): 3200-2900 (broad NH) and 1580 cm^{-1} (CO); ^{1}H-nmr (deuterioacetone): δ 3.73 (s, 3H), 6.43 (d, 1H, J = 2.5 Hz), 6.8-7.3 (m, 8H), 7.5-7.7 (m, 2H); exact mass m/e 277.113 (calcd. for $C_{18}H_{15}NO_2$ 277.110).

3-Benzoyl-4-phenyl-2-methylthiopyrrole (**7l**).

Reaction, analogously to **7k**, of **3e** (0.35 g, 1.2 mmoles) and chalcone (0.21 g, 1.0 mmoles) in 50 minutes and work-up as described for **7a**, resulted in a solid which was washed with ethyl ether-pentane (3:2) (10 ml) to give 0.21 g (73%) of **7l**, mp 167.5-170°. Recrystallization (twice) from ethyl ether-acetone (3:2) gave an analytically pure sample, mp 171-173° slight dec; ir (nujol): 3350 (NH) and 1615 cm^{-1} (CO); ^{1}H-nmr (deuterioacetone): δ 2.33 (s, 3H), 6.9-7.4 (m, 9H), 7.55-7.8 (m, 2H).

Anal. Calcd. for $C_{18}H_{15}NOS$: C, 73.70; H, 5.15; N, 4.77; S, 10.92. Found: C, 73.6; H, 5.2; N, 4.7; S, 10.9.

3-Carbomethoxy-4-phenyl-2-methylthiopyrrole (**7m**).

This compound was prepared analogously to **7k** from **3e** (0.69 g, 2.4 mmoles) and methyl cinnamate (0.32 g, 2.0 mmoles) to give (after washing with ethyl ether-pentane (3:7) (20 ml)) 0.36 g (72%) of **7m**, mp 106-108.5°. Crystallization from ethyl ether (charcoal) gave an analytically pure sample, mp 110-111.5°; ir (nujol): 3350 (NH) and 1675 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 3.72 (s, 3H), 6.64 (d, 1H, J = 3 Hz), 7.1-7.5 (m, 5H), 8.2-9.3 (m, 1H).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.31; N, 5.67; S, 12.96. Found: C, 63.3; H, 5.3; N, 5.6; S, 13.0.

3-Cyano-4-phenyl-2-methylthiopyrrole (**7n**).

Reaction of **3e** (0.70 g, 2.4 mmoles) and cinnamonitrile (0.26 g, 2.0 mmoles), and work-up as described for **7l**, gave 0.30 g (70%) of **7n**, mp 177.5-180°. An analytically pure sample was obtained by crystallization (twice) from dichloromethane-ethyl ether-pentane, mp 183-184.5°; ir (nujol): 3240 (NH) and 2220 cm^{-1} (C≡N); ^{1}H-nmr (deuterioacetone): δ 2.46 (s, 3H), 7.1-7.7 (m, 6H).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.71; N, 13.07; S, 14.96. Found: C, 67.1; H, 4.6; N, 13.2; S, 15.1.

3-Acetyl-4-methyl-2-methylthiopyrrole (**7o**).

A mixture of **3e** (0.87 g, 3.0 mmoles) and pent-3-en-2-one (90%, 0.28 g, 3.0 mmoles) was added to sodium hydride (60% in mineral oil, 0.40 g, 9 mmoles; the oil was removed previously with pentane) in DME (15 ml). After 50 minutes, work-up as described for **7a** gave 0.21 g (41%) of **7o**, mp 151-153°. Recrystallization (twice) from dichloromethane-ethyl ether (charcoal) gave an analytically pure sample, mp 153.5-155°; ir (nujol): 3330 (NH) and 1620 cm^{-1} (CO); ^{1}H-nmr (deuterioacetone): δ 2.25 (d, 3H, J = 1Hz), 2.46 (s, 3H), 2.54 (s, 3H), 6.6-6.75 (m, 1H).

Anal. Calcd. for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28; S, 18.94. Found: C, 56.8; H, 6.5; N, 8.2; S, 19.0.

Attempted Exchange of MeS for EtS in **3a**.

A solution of sodium ethanethiolate was prepared by addition of 0.5 ml of a solution of ethanethiol (4*N* in DME, 2.0 mmoles) to sodium hydride (0.13 g (*ca.* 3.0 mmoles) of a 60% suspension in mineral oil from which the oil was removed by washing with dry pentane under nitrogen). Five minutes after the evolution of hydrogen had stopped (in *ca.* 3 minutes), this solution was added with a syringe to the reaction mixture in DME (4

ml) formed in 15 minutes from **3a** (0.32 g, 1.0 mmole) and sodium hydride (0.086 g, *ca.* 2.0 mmoles, oil removed as above). After 25 minutes the mixture was worked up, as described for **7a**, to give 0.271 g of a brown-yellow oil which contained 52.5% of **3a** (determined in duplo by ^{1}H-nmr using dimethylsulfone as an internal standard). No signals of an ethyl group were observed.

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REFERENCES AND NOTES

(1) Present address: Department of Pharmacy, Groningen University.

(2) For a brief review on tosylmethyl isocyanide-chemistry see: A. M. van Leusen, in "Lectures in Heterocyclic Chemistry", Vol. 5, p. S 111, R. N. Castle and S. W. Schneller, Eds., HeteroCorporation, Orem, Utah 1980, (A Supplementary Issue of the *J. Heterocyclic Chem.*, Vol. 17); A. M. van Leusen and P. G. Oomkes, *Synth. Commun.*, **10**, 399 (1980); D. van Leusen and A. M. van Leusen, *Synthesis*, 325 (1980); S. P. J. M. van Nispen, C. Mensink and A. M. van Leusen, *Tetrahedron Letters*, 3723 (1980).

(3a) A. M. van Leusen, F. J. Schaart and D. van Leusen, *Rec. Trav. Chim.*, **98**, 258 (1979); O. Possel and A. M. van Leusen, *Heterocycles*, **7**, 77 (1977); (b) A. M. van Leusen and J. Schut, *Tetrahedron Letters*, 285 (1976).

(4) A. M. van Leusen, H. Jeuring, J. Wildeman and S. P. J. M. van Nispen, *J. Org. Chem.*, **46**, 2069 (1981). Meanwhile it has been established that **2** with Z = S reacts with aldehydes to give 2-thio-1,3-oxazoles, A. M. van Leusen and J. Boon, to be published.

(5) Part of this material was published in preliminary form: H. A. Houwing, J. Wildeman and A. M. van Leusen, *Tetrahedron Letters*, 143 (1976).

(6) J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947); J. W. Cornforth and H. T. Huang, *ibid.*, 1969 (1948).

(7) H. A. Houwing, J. Wildeman, and A. M. van Leusen, *J. Heterocyclic Chem.*, succeeding paper.

(8) Leading references on pyrrole ring syntheses: (a) A. Gossauer, "Die Chemie der Pyrrole", Springer Verlag, Berlin 1974; (b) R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London 1977; (c) B. M. Trost and E. Keinan, *J. Org. Chem.*, **45**, 2741 (1980); (d) A. M. van Leusen, H. Siderius, B. E. Hoogenboom and D. van Leusen, *Tetrahedron Letters*, 5337 (1972).

(9) Compound **3d** could not be formed by *O*-methylation of methyl *N*-(tosylmethyl)carbamate according to the method used for **3e**. Equally unsuccessful were attempts to methylate *N*-(tosylmethyl)benzamide (to **3**, L = MeO, A = Ph). For further details, see reference 11; compare also reference 24.

(10) *Cf.* N. H. Cromwell, P. L. Creger and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956); A. N. Nesmeyanov, L. V. Rybin, and M. I. Rybinskaya, *Izv. Akad. Nauk, S.S.S.R., Odt. Khim. Nauk*, 1451 (1961); *Chem. Abstr.*, **56**, 379 (1962).

(11) H. A. Houwing, Ph.D. thesis, Groningen, 1978.

(12) Reference 8a, p. 345.

(13) Compound **7k** was treated in the following ways: concentrated hydrogen chloride in methanol (*cf.* W. Siedel, *Ann. Chem.*, **544**, 144 (1943)); concentrated hydrogen iodide/phosphorus (S. Reiffers, Groningen University, personal communication); boron tribromide/water (*cf.* A. D. Fraser, S. J. Clark and H. H. Wotiz, *J. Org. Chem.*, **41**, 170 (1976)).

(14) L. Knorr and H. Lange, *Ber.*, **35**, 2998 (1902).

(15) E. Lipmaa, M. Mägi, S. S. Novikov, L. J. Khmelnitsky, A. S. Prihodko, O. V. Lebedev and L. V. Epshina, *Org. Magn. Reson.*, **4**, 153 (1972).

(16) O. Possel, Ph.D. thesis, Groningen, 1978.

(17) *Cf.* R. J. Abraham, R. D. Lapper, K. M. Smith and J. F. Unsworth, *J. Chem. Soc., Perkin Trans. II*, 1004 (1974).

(18) In the following discussion we will ignore the possibility of different pathways for the individual compounds **3**.

(19) *H-D* exchange was effected by reacting **3a** with sodium hydride (3 equivalents) in DME, followed by deuterium oxide after 15 minutes. Both methylene protons were replaced by deuterium according to nmr.

(20) Review: T. Kauffmann, *Angew. Chem.*, **86**, 715 (1974); *Angew. Chem., Int. Ed. Eng.*, **13**, 627 (1974).

(21) T. Olijnsma, J. B. F. N. Engberts and J. Strating, *Rec. Trav. Chim.*, **86**, 463 (1967).

(22) H. Meijer, R. M. Tel, J. Strating and J. B. F. N. Engberts, *ibid.*, **92**, 72 (1973).

(23) Commercial product from Ofichem., P. O. Box 24, Gieten, Holland; Procedure: B. E. Hoogenboom, O. H. Oldenziel and A. M. van Leusen, *Org. Synth.*, **57**, 102 (1977).

(24) T. Olijnsma and J. B. F. N. Engberts, *Synth. Commun.*, **3**, 1 (1973).

(25) J. B. F. N. Engberts, T. Olijnsma and J. Strating, *Rec. Trav. Chim.*, **85**, 1211 (1966).

(26) J. von Braun, *Ber.*, **35**, 3380 (1902).

(27) We acknowledge Mr. D. van Leusen for making available a sample of this material, prepared according to reference 8d.