Synthesis of 3,4-Disubstituted Pyrroles Bearing Substituents of Electron-Withdrawing and/or Electron-Donating Nature[1]

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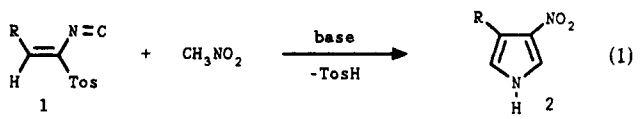
The synthesis is described of a series of 3,4-disubstituted pyrroles 8 from 1-isocyano-1-tosyl-1-alkenes and a variety of Michael donors. It is possible to use this method for the synthesis of pyrroles that bear no electron-withdrawing substituents.

After disclosure in 1972,[2] our tosylmethyl isocyanide (TosMIC) based synthesis of pyrroles has found ample application.[3] The protocol provides 3,4-disubstituted pyrroles from TosMIC and Michael acceptors, without the necessity of temporary use of protective groups at the unsubstituted positions 1, 2, and 5.[2,3] 2,3,4-Trisubstituted pyrroles are obtained similarly by employing various TosMIC derivatives.[2,3e,n] Recently, we have extended the scope of this line of the pyrrole syntheses with a one-step, high-yield preparation of 3-nitropyrroles **2**, using nitromethane and the condensation products[4] **1** of TosMIC and aldehydes (eq 1).[5] In this paper, we will show that the method can be adapted to the use of methane derivatives other than nitromethane.



Among the various pyrrole syntheses,[6a] few general applicable approaches exist to 3,4-disubstituted pyrroles. Thermal decarboxylation of 2-carboxylate- or 2,5-dicarboxylate-derived pyrroles has been used most often.[6a] 3,4-Diphenylpyrrole has been prepared in 90% yield from the corresponding 2,5-dicarboxylate,[6b] and more recently (in low yields) by photolysis of an appropriately substituted 1-ethenyl-1,2,3-triazole[6c] or by $TiCl_3$-mediated reduction of 2-phenyl-1-nitroethene.[6d] The yields of decarboxylations to 3,4-dialkylpyrroles usually are moderate,[6a,e] but reduction of acyl or ester side chains provide a useful alternative. Thus, 3,4-dimethylpyrrole was prepared from 3-carbethoxy-4-methylpyrrole.[3b] The same compound was obtained in moderate to low yields by application of the Piloty pyrrole synthesis[6a,f] or a modification thereof.[6g] Interestingly, this Baldwin modification[6g] has been extended also to the unsymmetrical 3-ethyl-4-methylpyrrole (opsopyrrole), albeit in 33% yield only. The decarboxylative[6e] and the reductive methods[6h] apply to opsopyrrole as well. An interesting ring-closing method of a 4-(tosylamino) acetal, prepared by the use of a new reagent *N*-(tosylmethyl)-*p*-toluenesulfonamide, was recently applied to opsopyrrole also.[6i]

Results and Discussion

We have been unable to realize the synthesis of 3-cyanopyrroles by direct extrapolation from eq 1, i.e., by using acetonitrile instead of nitromethane. In fact, reaction of **1** (R = Ph) and acetonitrile, analogous to eq 1, gave an unattractive reaction mixture in which no 3-cyano-4-phenylpyrrole (**8a**) was detected (using 1.25 equiv of $CH_3C{\equiv}N$ and 1.5 equiv of *t*-BuOK in 1,2-dimethoxyethane, 20 °C, 1 h). Why does an equal approach apply to nitromethane and not to acetonitrile?

The synthesis of 3-nitropyrroles was rationalized previously as the result of a Michael addition of the conjugate base of nitromethane followed by ring closure of the resulting enolate anion **5** to the isocyano carbon,[5] as in Scheme I with Z = NO_2 and H instead of COR′. The dichotomy in results obtained with nitromethane and acetonitrile could be a reflection of the large difference of their pK_a values[7] (ca. 10 and 25, respectively). Carbanions **3** as well as **4** and **5** are important intermediates in Scheme I. If the assumption were correct, temporarily increased acidity of the acetonitrile protons possibly would permit the synthesis of 3-cyanopyrroles. Obviously, an additional acidifying substituent in acetonitrile needs to be removed in the course of the process, because in the ultimate products all three hydrogens of nitromethane or acetonitrile are replaced by carbon, carbon bonds (eqs 1 and 2 and Scheme I).

This concept has worked out beautifully in actual practice. A quantitative yield of 3-cyano-4-phenylpyrrole

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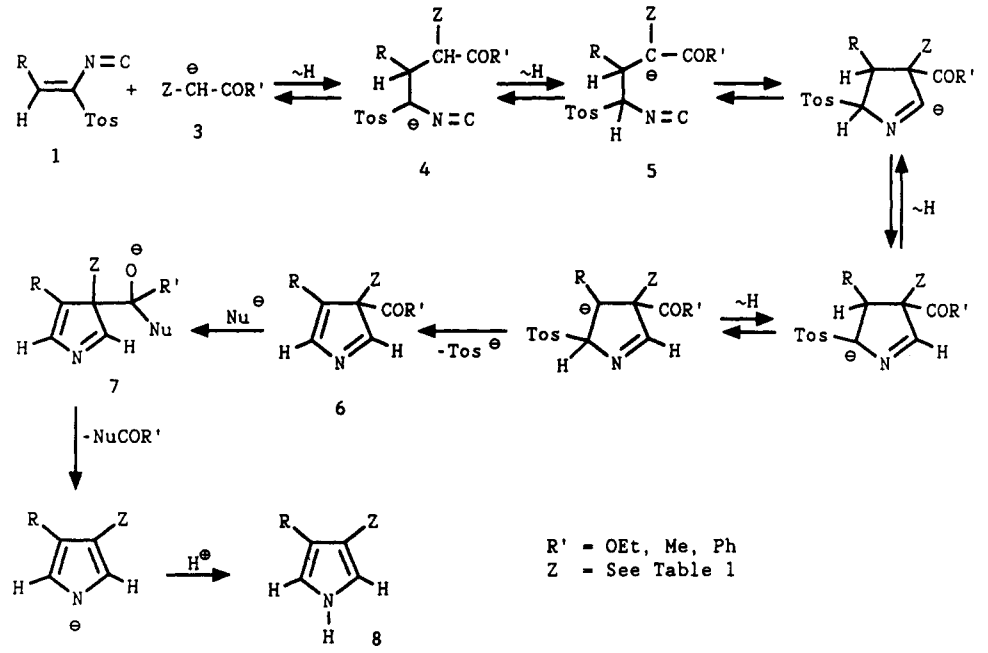
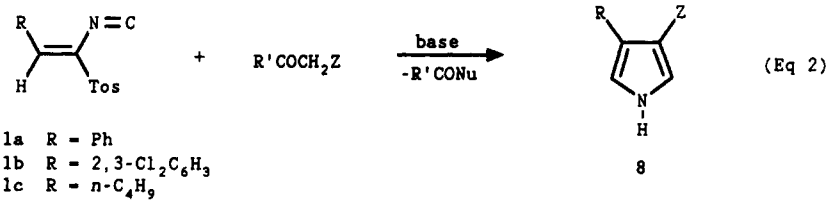
Scheme I[a]



[a] We have arbitrarily chosen for elimination of *p*-toluenesulfinic acid (TosH) prior to removal of the temporarily acidifying substituent COR'. The same results, however, are obtained when this order is reversed.

Table I



1a R = Ph
1b R = 2,3-$Cl_2C_6H_3$
1c R = *n*-C_4H_9

8

entry	starting materials: isocyanide	starting materials: R'COCH$_2$Z	product 8: compd	R	Z	yield (%)	mp (°C)
1	1a	EtOOCCH$_2$C≡N	8a	Ph	C≡N	99	123–126[a]
2	1a	CH$_3$C≡N[b]	8a	Ph	C≡N	0	
3	1b	EtOOCCH$_2$C≡N	8b	2,3-$Cl_2C_6H_3$	C≡N	93	152–153[c]
4	1a	EtOOCCH$_2$COOEt	8c	Ph	COOEt	70	118–122
5	1a	CH$_3$COOEt[b]	8c	Ph	COOEt	0	
6	1a	CH$_3$COCH$_2$COOEt	8c	Ph	COOEt	92	118–122
7	1c	CH$_3$COCH$_2$COOEt	8d	n-Bu	COOEt	62	oil
8	1a	CH$_3$COCH$_2$COCH$_3$	8e	Ph	COCH$_3$	86	156–158
9	1a	PhCOCH$_2$COPh	8f	Ph	COPh	61	232–234[d]
10	1a	CH$_3$COPh[b]	8f	Ph	COPh	57	232–234[d]
11	1a	PhCOCH$_2$CH$_3$	8g	Ph	CH$_3$	73	oil
12	1a	EtOOCCH$_2$Ph	8h	Ph	Ph	57	92–95[e]
13	1c	PhCOCH$_2$CH$_3$	8i	n-Bu	CH$_3$	33	oil

[a] Lit.[2] mp 128–129 °C. [b] R'CO = H. [c] Lit.[9] mp 152–153 °C. [d] Lit.[2] mp 229–231 °C. [e] Lit.[6b] mp 99 °C.

(**8a**) was achieved by reaction of **1a** and ethyl cyanoacetate (pK_a ca. 12)[7] instead of acetonitrile (eq 2, Table I, entries 1 versus 2). The result is explained by Scheme I (with R' = OEt). Analogous observations were made in the pair of reactions of **1a** with ethyl acetate (pK_a ca. 25),[7] which gave no pyrrole (entry 5), and with diethyl malonate (pK_a ca. 13),[7] which gave 3-carbethoxy-4-phenylpyrrole (**8c**) in 70% yield (entry 4). On the other hand, 3-benzoyl-4-phenylpyrrole (**8f**) was obtained, analogously to 3-nitropyrroles, from acetophenone and **1a** in 57% yield (entry 10). Apparently, acetophenone (pK_a ca. 20)[7] is sufficiently acidic to perform the reaction without assistance of an additional acidifying group. The yield of **8f** was slightly improved (to 61%) when acetophenone was replaced by dibenzoylmethane, acting as an acetophenone equivalent equipped with an additional acidifying benzoyl group (entry 9).

It is not entirely clear as to how pK_a differences of the reagents are involved in the proposed mechanism (Scheme I). Obviously, the ring closing reaction (from **5**) forms an important step in a series of coupled equilibria. Enhanced electronegativity of Z would help to shift equilibrium **4** ⇄ **5** to the right, possibly facilitating the ring closure of **5**.

Entries 6–9, 11, and 13 show that acetyl and benzoyl groups also are useful acidifying auxiliaries, and entries 6 and 7 demonstrate that the acetyl group is removed in preference over ester groups, reflecting the greater susceptibility of the acetyl group to nucleophilic attack (Scheme I, **6** → **7**).

All pyrroles synthesized previously with the use of TosMIC and Michael acceptors[2,3] bear at least one

(strongly) electron-withdrawing substituent (at C-3). The present application of acidifying auxiliary groups makes it possible to synthesize pyrroles without electron-withdrawing substituents at C-3, such as 3-methyl-4-phenylpyrrole (**8g**, entry 11) and 3-butyl-4-methylpyrrole (**8i**, entry 13), using propiophenone as an activated form of "methylated methane". Note the striking difference with the reaction of acetophenone (entry 10), where the benzoyl group is retained in the product **8f**. Scheme I readily explains the difference. When, in the reaction of acetophenone, the stage of intermediate **6** (R′ = Ph) is reached, a 1,3-hydrogen shift (Z = H) will straight away lead to 3-benzoyl-4-phenylpyrrole (**8f**) as a departure of the last three steps of Scheme I. Obviously, a similar hydrogen shift is not possible in the reaction of propiophenone, and the routine of Scheme I is followed for **6** (Z = Me) to give 3-methyl-4-phenylpyrrole (**8g**) and 3-butyl-4-methylpyrrole (**8i**). In an analogous reaction (entry 12), the ester group was used to temporarily increase the acidity of toluene to produce 3,4-diphenylpyrrole (**8h**).

Furthermore, we have successfully applied the new method to synthesize 3-cyano-4-(2′,3′-dichlorophenyl)-pyrrole (**8b**, entry 3), which recently has found application as a new seed-protecting agent (fenpiclonil),[8] previously prepared from ethyl α-cyano-2,3-dichlorocinnamate and TosMIC.[9]

Starting materials **1a**, **b**, and **c** formally are Knoevenagel condensation products of TosMIC and aldehydes, which are easily prepared from these compounds.[2,4b] Recently, we have shown that this preparation even applies to sterically hindered ketones such as pinacolone.[10] Consequently, a wide variety of compounds **1** is now available, including **1b** and **1c** which are new representatives prepared for the present study.

A number of compounds **8** (Table I) have been prepared previously. By way of illustration we will compare the different methods used for the synthesis of 3-cyano-4-phenylpyrrole (**8a**). This compound was first prepared in 35% yield from TosMIC and cinnamonitrile (the condensation product of benzaldehyde and acetonitrile).[2] In the present method benzaldehyde is first condensed with TosMIC to give **1a**,[2,4b] which, next, fails to react with acetonitrile. However, ethyl cyanoacetate (instead of acetonitrile) gives a quantitative yield of **8a** in reaction with **1a** (Table I, entry 1). This clearly underlines the profitable use of the ester auxiliary in the nitrile-bearing reaction partner. Further, a Japanese patent describes the reaction of ethyl 2-cyanocinnamate with TosMIC to **8a** in 89% yield.[9] (Note that ethyl 2-cyanocinnamate is the condensation product of benzaldehyde and ethyl cyanoacetate). We have used this alternative approach to the synthesis of 3-carbethoxy-4-phenylpyrrole (**8c**, 60% yield) from diethyl benzalmalonate and TosMIC (see Experimental Section). Hence, there are two ways to employ acidifying auxiliaries to make the unsuccessful combination of the three basic components (benzaldehyde, TosMIC, and acetonitrile) a successful one.

Experimental Section

General. All experiments were carried out under nitrogen. ^{1}H NMR spectra were recorded on a 60-MHz Hitachi Perkin-Elmer R-24B apparatus. ^{13}C and 300-MHz ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 841 infrared or a 257 grading spectrophotometer. Melting points, taken in a silicone oil bath, are uncorrected. Elemental microanalyses were carried out in the Analytical Department of our laboratory. Mass spectra were obtained on a AEI MS-902 instrument.

(*E*)-*N*-[2-(2,3-Dichlorophenyl)-1-tosylethenyl]formamide. A solution of TosMIC (4.90 g, 25.0 mmol) in dry 1,2-dimethoxyethane (DME, 20 mL) was added dropwise to a stirred suspension of *t*-BuOK (4.0 g, ca. 0.3 mmol) in DME (25 mL) at −50 °C. A solution of 2,3-dichlorobenzaldehyde (4.38 g, 25 mmol) in DME (10 mL) was added while the temperature was kept below −40 °C. After being stirred for 10 min at −40 °C the mixture was poured into 5% aqueous NH_4Cl (150 mL). The solid was collected, washed with water and MeOH (25 mL), and dried in vacuum to give 7.9 g (85%) of the title formamide,[12] mp 189–193 °C. Crystallization from MeOH raised the mp to 192–193 °C: IR (Nujol) 3136 (NH), 1673 (C=O), 1318 and 1154 cm^{-1} (SO_2). Anal. Calcd for $C_{16}H_{13}Cl_2NO_3S$ (370.25): C, 51.90; H, 3.54; Cl, 19.15; N, 3.78; S, 8.66. Found: C, 52.15; H, 3.51; Cl, 19.21; N, 3.77; S, 8.73.

(*E*)-2-(2,3-Dichlorophenyl)-1-isocyano-1-tosylethene (1b). To a cold suspension of (*E*)-*N*-[2-(2,3-dichlorophenyl)-1-tosylethenyl]formamide (0.925 g, 2.5 mmol) in DME (10 mL) at −40 °C was added Et_3N (1.75 mL, 12.5 mmol) and subsequently $POCl_3$ (0.25 mL, 2.7 mmol). The mixture was stirred for 1 h between −10 and −30 °C before it was poured in an aqueous 1% NH_4Cl solution (100 mL). By extraction with CH_2Cl_2 (3 × 25 mL), filtration of the combined extracts over alumina, concentration, and one crystallization from MeOH, 0.46 g (52%) of **1b** was obtained,[12] mp 102 °C dec; IR (Nujol) 2093 (N=C), 1334, 1160 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3), 6.90–8.20 (m, 8). Anal. Calcd for $C_{16}H_{11}Cl_2NO_2S$ (352.23): C, 54.56; H, 3.15; Cl, 20.13 N, 3.98; S, 9.10. Found: C, 54.54; H, 3.57; Cl, 20.05; N, 3.86; S, 8.73.

(*E*)-*N*-(1-Tosyl-1-hexenyl)formamide. A solution of TosMIC (3.90 g, 20 mmol) in dry DME (20 mL) was added dropwise to a stirred suspension of *t*-BuOK (3.0 g, ca. 25 mmol) in dry DME (10 mL) at a temperature between −50 and −40 °C. A solution of valeraldehyde (3.0 mL, 28 mmol) in DME (10 mL) was added slowly at a temperature between −50 and −40 °C. After being stirred for 10 min at −50 °C the mixture was poured in 5% aqueous NH_4Cl (200 mL). By extraction with CH_2Cl_2 (60, 30, and 20 mL), washing with brine, drying (Na_2SO_4), concentrating, and treatment of the residue with 15 mL of MeOH at −20 °C, 3.75 g (67%) of the title formamide was obtained,[11] mp 83–84 °C: IR (Nujol) 3236 (NH), 1680 (C=O), 1650 (C=C), 1314 and 1154 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 0.7–1.1 (m, 3), 1.1–1.8 (m, 4), 2.0–2.7 (m, 5), 2.41 (s), 6.8–8.2 (m, 7). Anal. Calcd for $C_{14}H_{19}NO_3S$ (281.372): C, 59.76; H, 6.81; N, 4.98; S, 11.39. Found: C, 59.54; H, 6.85; N, 5.03; S, 11.34.

(*E*)-1-Isocyano-1-tosyl-1-hexene (1c). $POCl_3$ (0.2 mL, 2.1 mmol) was slowly added to a solution of (*E*)-*N*-(1-tosyl-1-hexenyl)formamide (0.562 g, 2.0 mmol) and Et_3N (1.4 mL, 10 mmol) in dry THF (10 mL) at −30 °C. After being stirred for 10 min the mixture was poured in 5% aqueous NH_4Cl (50 mL). By extraction with EtOAc (20 mL), washing with brine, drying (Na_2SO_4), concentrating, treatment of the residue with MeOH (5 mL), and storing −20 °C for 2 h, 0.260 g (50%) of **1c** was obtained; mp 56–60 °C. Analytically pure **1c** was obtained by one additional crystallization from MeOH,[11] mp 58–60 °C: IR (Nujol) 2117 (N=C), 1630 (C=C), 1339, 1166 and 1144 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 0.7–1.1 (m, 3), 1.1–1.6 (m, 4), 2.2–2.7 (m, 5), 2.45 (s), 7.03 (t, J = 8 Hz, 1), 7.30, 7.43, 7.77, 7.90 (AB-q, 4). Anal. Calcd for $C_{14}H_{17}NO_2S$ (263.357): C, 63.85; H, 6.51; N, 5.32; S, 12.17. Found: C, 63.68; H, 6.60; N, 5.32; S, 11.15.

3-Cyano-4-phenylpyrrole[2] (8a). According to eq 2, Entry 1. To a solution of ethyl cyanoacetate (0.28 g, 2.5 mmol) in absolute ethanol (10 mL) was added sodium (0.05 g, 2.2 mmol). When this reaction was complete (*E*)-1-isocyano-2-phenyl-1-to-

(8) Brighton Crop Protection Conference. Pest and Deseases Vol. 1; Proceed. Intern. Conf. British Crop Protection Council, Brighton, U.K., Nov 1988.

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(11) The *E*-configuration was assigned by extrapolation which has been discussed earlier (Ref.4).

(12) Following an improved procedure,[2] which uses 2 equiv of *t*-BuOK as developed by F. R. Leusink (personal communication).

sylethene[4] (**1a**, 0.566 g, 2.00 mmol) was added. After being stirred for 30 min at rt, the mixture was poured into ice–water (80 mL). After 10 min the solid was collected, washed with water, and dried in vacuum to give 0.335 g (99%) of **8a**, mp 114–124 °C. By sublimation (0.01 mm Hg) 0.30 g of **8a** was obtained, mp 123–126 °C; mixed mp with material obtained previously from cinnamonitrile and TosMIC (below) showed no depression: IR (Nujol) 3360 (NH), 2290 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 6.87 (triplet-like signal, J = 2 Hz, 1), 7.1–7.8 (m, ca. 6), 9.0 (br. signal, 1). **Using TosMIC.**[12] To a stirred suspension of t-BuOK (1.05 g, ca. 13 mmol) in THF (10 mL) at −30 °C was added in 2 min a solution of TosMIC (1.17 g, 6.0 mmol) in THF (10 mL). The temperature rose to −25 °C. The mixture was stirred for 4 min at −30 °C before a solution of cinnamonitrile (0.77 g, 6.0 mmol) in THF (10 mL) was added over 4 min. Stirring was continued for 15 min at −10 °C, and then the mixture was poured on 50 g of ice. Most of the THF was removed while the temperature was kept below 35 °C. The off-white precipitate was collected, washed with water, and dried in vacuum to give 0.89 g (88%) of **8a**, mp 124–125 °C (lit.[2] mp 128–129 °C; 35% yield).

3-Cyano-4-(2,3-dichlorophenyl)pyrrole[8,9] (8b). Powdered NaOH (0.07 g, 1.8 mmol) was added to a stirred solution of ethyl cyanoacetate (0.23 g, 2.0 mmol) in 10 mL of ethanol. After 10 min, isocyanide **1b** (0.53 g, 1.5 mmol) was added and stirring was continued for 1 h at rt. The mixture was poured into ice–water (100 mL). The solid was collected, washed with water, and dried in vacuum to give 0.33 g (93%) of **8b**, mp 135–150 °C. After one crystallization from CH_2Cl_2/petroleum ether (bp 40–60 °C) it showed a mp of 152–153 °C (lit.[9] mp 152–153 °C): IR (Nujol) 3586 (NH), 2226 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 6.95 (triplet-like signal, J = 2 Hz, 1), 7.1–7.8 (m, ca. 4), 8.9 (br. signal, 1).

3-Carbethoxy-4-phenylpyrrole (8c, According to eq 2, Entry 6) was prepared analogously to **8a** from isocyanide **1a** (0.566 g, 2.0 mmol) and ethyl acetoacetate (0.325 g, 2.5 mmol) in a yield of 0.394 g (92%), mp 118–122 °C: IR (Nujol) 3350 (NH), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3), 4.11 (q, J = 7 Hz, 2) 6.51 (triplet-like signal, J = 2 Hz, 1), 7.0–7.5 (m, ca. 6), 8.8 (br signal, 1); exact mass calcd for $C_{13}H_{13}NO_2$ m/e 215.095, found 215.093. Similarly, pyrrole **8c** (eq 2, entry 4) was prepared from isocyanide **1a** and diethyl malonate (0.400 g, 2.5 mmol) in place of ethyl acetoacetate in a yield of 0.24 g (70%), mp 121–124 °C. Alternatively, pyrrole **8c** was prepared following the procedure of ref 8 by adding powdered NaOH (0.5 g, 12 mmol) to a stirred mixture of diethyl benzalmalonate (1.24 g, 5.0 mmol) and TosMIC (1.025 g, 5.3 mmol) and EtOH (25 mL) at 0 °C. After the solution was stirred for 1 h at 0 °C an additional portion of TosMIC (0.14 g, 0.70 mmol) was added and stirring was continued for 1 h at 20 °C. The reaction mixture was poured into ice–water (500 mL) and was stirred for 10 min. The solid was collected, washed with water, and dried in vacuum to give 0.760 g of crude **8c**, mp 113–125 °C. Sublimation (0.02 mmHg, 120 °C) gave 0.650 g (60%) of **8c**, mp 121–124 °C. This material was identical (by IR and ^1H NMR) with a sample described above.

3-*n*-Butyl-4-carbethoxypyrrole (8d). t-BuOK (0.120 g, ca. 1 mmol) was added to a solution of isocyanide **1c** (0.263 g, 1.0 mmol) and ethyl acetoacetate (0.160 g, 1.3 mmol) in absolute ethanol (5 mL). After being stirred for 1 h at 20 °C, the mixture was poured into 5% aqueous NH_4Cl (40 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give an oil, which was passed rapidly through a short column of alumina (4- × 3-cm i.d., using 50 mL of CH_2Cl_2). After removal of the solvent the residue was distilled using a short-path distillation apparatus (bath temperature 80–120 °C, 0.1 mmHg) to give 0.115 g (62%) of **8d**: IR (neat) 3324 (NH), 1682 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.7–1.9 (m, 10), 2.73 (t, br, J = 7 Hz, 2), 4.28 (q, J = 7 Hz, 2), 6.45–6.66 (m, 1), 7.39 (triplet-like signal, J = 2 Hz, 1), 8.9 (br signal, 1); exact mass calcd for $C_{11}H_{17}NO_2$ m/e 195.126, found 195.126.

3-Acetyl-4-phenylpyrrole[2] (8e). Powdered NaOH (0.08 g, 2.0 mmol) was added to a stirred suspension of **1a**[4] (0.425 g, 1.5 mmol) and acetylacetone (0.19 g, 1.9 mmol) in methanol (7.5 mL) at 20 °C. The reaction mixture was stirred for 2.5 h, and then water (15 mL) was added slowly. The solid, collected after storing the mixture for 20 h at −20 °C, was washed with water and dried in vacuum to give 0.24 g (86%) of **8e**, mp 140–150 °C. After one crystallization from CH_2Cl_2/petroleum ether (bp 40–60 °C), mp 156–158 °C (lit.[2] mp 157–158 °C): IR (Nujol) 3326 (NH), 1646 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.34 (s, 3), 6.70 (triplet-like signal, J = 2 Hz, 1), 7.2–7.7 (m, ca. 6), 8.8 (br signal, 1).

3-Benzoyl-4-phenylpyrrole[2] (8f, According to eq 2, Entry 10). t-BuOK (0.20g, 1.8 mmol) was added to a solution of acetophenone (0.12 g, 1.0 mmol) in DME (5 mL) at 0 °C. This mixture was stirred for 10 min at 0 °C, and then **1a**[4] (0.283 g, 1.00 mmol) was added and the ice bath was removed. After being stirred for 1 h the mixture was poured into ice–water (50 mL). The solid was collected, washed with water, and dried in vacuum to give 0.25 g of crude product which was purified by column chromatography on alumina (activity grade II–III; CH_2Cl_2) followed by one crystallization from CH_2Cl_2 to give 0.14 g (57%) of **8f**, mp 223–226 °C; mixed mp using the material obtained from chalcone and TosMIC[2] (see below) showed no depression: IR (Nujol) 3310 (NH), 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$/CF_3COOH) δ 6.84 (triplet-like signal, J = 2 Hz, 1), 7.10–7.80 (m, ca. 11), 9.4 (br signal, 1). **According to eq 2, Entry 9.** Powdered NaOH (0.10 g, 2.5 mmol) was added to a stirred solution of dibenzoylmethane (0.450 g, 2.0 mmol) in methanol (10 mL). After 10 min **1a**[4] (0.566 g, 2.0 mmol) was added, and the mixture was refluxed for 5 min. After 3 h of stirring at 20 °C, the mixture was poured in water (50 mL). The solid was collected washed with MeOH (10 mL) and dried in vacuum to give 0.30 g (61%) of **8f**, mp 231–234 °C, identical by IR and ^1H NMR with material described above. **From TosMIC.** *N*-Benzyltrimethylammonium hydroxide (40% in MeOH, 5 mL, 12 mmol) was added all at once to a stirred solution of TosMIC (1.00 g, 5.1 mmol) and chalcone (1.04 g, 5 mmol) in THF (25 mL) at 20 °C. After 15 min water (100 mL) was added. The solid was collected, washed with MeOH (10 mL), and dried in vacuum to give 1.09 g (88%) of **8f**, mp 232–234 °C.

3-Methyl-4-phenylpyrrole (8g). A solution of isocyanide **1a** (0.566 g, 2.0 mmol) and propiophenone (0.536 g, 4 mmol) in DME (10 mL) was added over 10 min to a mixture of t-BuOK (0.70 g, (6.2 mmol) and DME (5 mL) at 0 °C and stirred for 1 h at 20 °C. MeOH (0.5 mL) was added, and the mixture was stirred for another 5 min and then poured into ice–water (80 mL). This mixture was extracted with CH_2Cl_2 (30, 20 and 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. By column chromatography on alumina (activity grade II–III, diethyl ether/petroleum ether (bp 40–60 °C) (1:5)) was obtained 0.23 g (73%) of **8g** as a colorless oil: IR (neat) 3500 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3), 6.19–6.38 (m, 1), 6.49 (triplet-like signal, J = 2 Hz, 1), 6.7–8.0 (m, ca. 6); exact mass calcd for $C_{11}H_{11}N$ m/e 157.089, found 157.092.

3,4-Diphenylpyrrole[6b] (8h). A solution of **1a**[4] (0.283, 1.0 mmol) in DME (3 mL) was added in 30 min to a solution of ethyl phenylacetate (0.328 g, 2.0 mmol) and t-BuOK (0.25 g, 2.2 mmol) in DME (5 mL) at 0 °C and stirred for 1 h at 20 °C. The brown reaction mixture was poured into ice–water (50 mL) and then extracted with CH_2Cl_2 (25, 15, and 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. By column chromatography (alumina, activity grade III; diethyl ether/petroleum ether (bp 40–60 °C)) was obtained 0.25 g (57%) of **8h** as a glassy substance. By short-path distillation (0.1 mm, bath temperature 100 °C) was obtained **8h** as as a solid, mp 80–92 °C. Further purification by crystallization from $CHCl_3$/petroleum ether (bp 40–60 °C) raised the mp to 92–95 °C (lit.[6b] mp 99 °C): IR (Nujol) 3520 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 6.75 (d, J = 2 Hz, 2), 7.22 (s, 5), 8.0 (br signal, 1).

3-Butyl-4-methylpyrrole (8i) was prepared analogously to **8g** from isocyanide **1c** (0.526 g, 2.0 mmol) and propiophenone (0.536 g, 4 mmol). After chromatography and short-path distillation (13 mm, bath temperature 60 °C) was obtained 0.09 g (33%) of **8i** as a colorless oil. The compound is unstable in air: IR (neat) 3399 cm^{-1} (NH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, J = 7 Hz, 3), 1.46–1.70 (m, 4), 2.15 (s, 3), 2.53 (t, J = 8 Hz, 2), 6.58 (m, 2), 7.77 (br signal, 1); ^{13}C NMR ($CDCl_3$) δ 9.90 (q), 13.87 (q), 22.54 (t), 24.84 (t), 32.48 (t), 114.77 (d), 115.42 (d), 117.37 (s), 123.38 (s); exact mass calcd for $C_9H_{15}N$ m/e 137.120, found 137.120.

Registry No. **1a**, 71333-60-3; **1b**, 139276-29-2; **1c**, 139276-30-5; **8a**, 40167-37-1; **8b**, 74738-17-3; **8c**, 64276-62-6; **8d**, 139276-31-6; **8e**, 40167-28-0; **8f**, 40167-32-6; **8g**, 116267-86-8; **8h**, 1632-48-0; **8i**,

139276-32-7; $EtOOCCH_2C{\equiv}N$, 105-56-6; $CH_3C{\equiv}N$, 75-05-8; $EtOOCCH_2COOEt$, 105-53-3; CH_3COOEt, 141-78-6; CH_3COCH_2COOEt, 141-97-9; $CH_3COCH_2COCH_3$, 123-54-6; $PhCOCH_2COPh$, 120-46-7; CH_3COPh, 98-86-2; $PhCOCH_2CH_3$, 93-55-0; $EtOOCCH_2Ph$, 101-97-3; 2,3-dichlorobenzaldehyde, 6334-18-5; (*E*)-*N*-[2-(2,3-dichlorophenyl)-1-tosylethenyl]formamide, 139276-33-8; valeraldehyde, 110-62-3; (*E*)-*N*-(1-tosyl-1-hexenyl)formamide, 139276-34-9.

Chemistry of *N,P*-Acetals: Application to the Synthesis of 20-Ketosteroids

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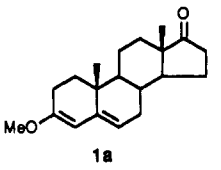
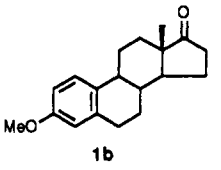
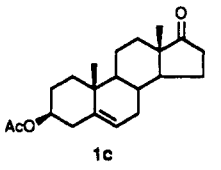
A series of new derivatives of α-(isocyanomethyl)phosphonates (**6a,b,c** and **9**) is described, which are formed by methylation of (*E*)-17-[(diethylphosphono)isocyanomethylene] steroids **5a,b,c** and 17β-[(diethylphosphono)isocyanomethyl] steroid **8**. It proved possible to hydrolyze these compounds under relatively mild conditions to 20-ketosteroids **7a,b,c** and **10**, showing for the first time that geminal N- and P-substituted carbon compounds do react as *N,P*-acetals.

Acetals contribute valuable functionality to organic synthesis.[2,3] *O,O*-Acetals are particularly useful as protected aldehydes and ketones, which are deprotected by mild acid hydrolysis.[2a,b] *S,S*-Acetals are important acyl anion equivalents ("reversal of polarity"), and are hydrolyzed to carbonyl compounds under oxidative conditions.[2c,d] Acid hydrolysis of other types of acetals (e.g., *O,S*-,[3a-e] *N,S*-,[3a,b,f-l,14] *N,N*-,[3a,b,m,n] and *N,O*-acetals[3a,b,o]) has been described also. Remarkably, compounds with geminal N and P substituents attached to carbon have so far not been recognized as acetals. It is the purpose of this paper to demonstrate *N,P*-acetal behavior of such compounds.

We have synthesized a series of new derivatives of α-(isocyanomethyl)phosphonates starting with compounds **5**. These compounds are converted by allylic alkylation to *N,P*-acetals **6** (Scheme I) and by reduction followed by alkylation to *N,P*-acetal **9** (Scheme II). With aqueous $HClO_4$, compounds **6** and **9** proved to hydrolyze to the corresponding ketones **7** and **10**, showing for the first time that *N,P*-acetal behavior is feasible indeed. So far, derivatives of α-(aminomethyl)phosphonates, carrying masked amino groups, have been hydrolyzed to stages no further than amino phosphonate esters or acids,[4] which, in the present context, means a conversion of one type of *N,P*-acetal into the other. In 1984, Diel and Maier[4e] stated with respect to the hydrolysis of esters of 1-isocyanocyclopropane-1-phosphonic acid and 1-(benzylideneamino)cyclopropane-1-phosphonic acid that "by *complete* (italics by J.S. et al.) hydrolysis with concentrated hydrochloric acid at 100 °C one obtains...in quantitative yield 1-aminocyclopropane-1-phosphonic acid."[5]

We have applied the *N,P*-acetal chemistry to steroid derivatives **5**, which were needed for other synthetic applications.[6] Basically known chemistry was used to develop a practical synthesis of the formal Knoevenagel condensation products **5** from 17-oxosteroids **1** and diethyl (isocyanomethyl)phosphonate[7] (**2**). Schöllkopf et al.[7] have reported that the formation of oxazolines of type **3** is possible only with aldehydes and with acetone, using copper(I) oxide in benzene. However, by using KH in

Table I. Yields of Compounds 4a–c to 7a–c Depicted in Scheme I and Derived from Steroids 1a–c

steroids 1	yield[a] (%) of compds 4	5	6	7	overall
 **1a**	70	98	92	86[b]	54
 **1b**	70	84	90	76	40
 **1c**	76	60	95	71[c]	31

[a] Yields of isolated purified materials based on **1** in the case of **4**, and further on the next lower compound numbers. [b] 3,5-Dienol ether group was hydrolyzed to 4-en-3-one. [c] 3β-Acetoxy group was hydrolyzed to 3β-hydroxy.

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