NEW METHODS FOR THE SYNTHESIS OF 2-ARYLPYRROLES

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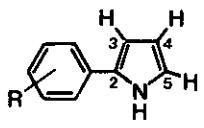
Abstract - Two short and efficient synthetic approaches for -mostly unknown- 2-arylpyrroles are presented. The key intermediates 3 are conveniently obtained from commercially available acetophenones 5 *(method I) or benzoic* acid derivatives 10, 11 (method II).

In connection with a synthetic program directed at psychoactive compounds[1] we needed a short, efficient synthesis for 2-phenylpyrroles 1, applicable for large scale preparations. Also a wide *variety of substituents* R and replacement of 2-phenyl by heteroaryl groups should be allowed.



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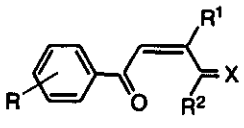


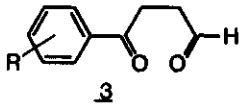
2a-d

	X	R^1	R^2
a	$NO_2^{\ominus}K^{\oplus}$	H	H
b	$NNMe_2$	H	H
c	$NNMe_2$	OH	H
d	H_2	H	Cl

Only a few 2-phenylpyrrole syntheses described in literature give rise to 3,4,5-unsubstituted derivatives. Methods based on formation of the C2-N bond by cyclization reactions were described by Severin[2a-c], using 1-phenylbut-2-en-1-one derivatives 2a, 2b, and 2c. Similarly, chlorobutenones 2d were described as precursors by Rosenmund[3]. Other strategies are also based on intramolecular condensation reactions forming either the C2-C3 bond (ringclosure of N-allylbenzamides)[4] or the C3-C4 bond (treatment of acetophenone oxime vinyl ethers with strong base)[5]. Wittig[6a] and Saeki[6b] employed intermolecular C2-phenyl bond connections using benzyne and phenyldiazonium salts, respectively. None of these methods met our criteria because of at least one of the following disadvantages: lack of general applicability, poor yields or drastic reaction conditions.

A more attractive approach seemed to be the Paal-Knorr cyclization of 4-oxobenzenebutanal (3, R=H) with ammonium acetate, reported by Berner[7]. However, little is known about the accessibility of precursors of type 3. This is surprising in view of the large number of synthetic methods for 1,4-dicarbonyl compounds in general, but these mainly apply to 1,4-diketones[8]. Only in recent years a number of methods towards 4-oxoalkanals 4 have been published[9-14], but these have not been applied to the aryl analogues 3.

We now report on two new, straightforward synthetic routes to 4-oxo-arylbutanals 3 and the corresponding pyrroles 1 starting from commercially available reagents.



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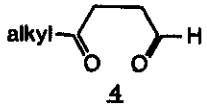
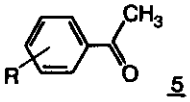


4

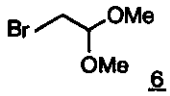
Published methods for the construction of the 4-oxobutanal moiety of 4 make use of either rearrangement reactions [9] or different types of C-C connections using one of the following synthon combinations: C_0(donor) + C_4(acceptor)[10], C_1(d)+C_3(a)[11], C_1(a)+C_3(d)[12] or C_2(d)+C_2(a)[13,14]. Application of these principles to the synthesis of the phenyl substituted series 3 and translation of the appropriate synthons into commercially available reagents resulted in two possible approaches.

Method I, C_2(d)+C_2(a) connection. Substituted acetophenones 5 and bromoacetal 6 were chosen as potentially useful C_2(d) and C_2(a) reagents, respectively. However, 6 is known to be a poor electrophile[15] and a first attempt to alkylate lithiated acetophenone (5, R=H) with 6 resulted in proton transfer only. Since lithiated N-substituted imino derivatives of



5

C2(d)



6

C2(a)

alkyl methyl ketones are reported to be excellent nucleophiles [16], even towards 6[17], we first converted 5 into the corresponding N,N-dimethylhydrazones 7[18]. Lithiation of 7 was effected by treatment with n-butyllithium in THF at -30°C for 30 min. After addition of 6

alkylation proceeded slowly at 20°C (16 h), giving hydrazone acetals 8 in good yields (see Table I). These results illustrate the excellent nucleophilic properties of lithiated hydrazones compared to the corresponding enolates. In most cases small amounts of starting hydrazones 7 were recovered, presumably formed by a (minor) proton transfer process. Addition of DMSO before alkylation resulted in increased amounts of 7. Both carbonyl protecting groups in 8 were removed conveniently in one step by treatment with hydrochloric acid in THF-H_2O at 20°C for 1 h. The resulting 4-oxo-arylbutanals 3 were converted directly into 1 in good overall yields using Berner's procedure[7] (see Table I).

This three-step procedure is suitable for large scale preparations as was shown by the synthesis of over 100 g quantities of 1b.

Method I C2(d)+C2(a) fragments

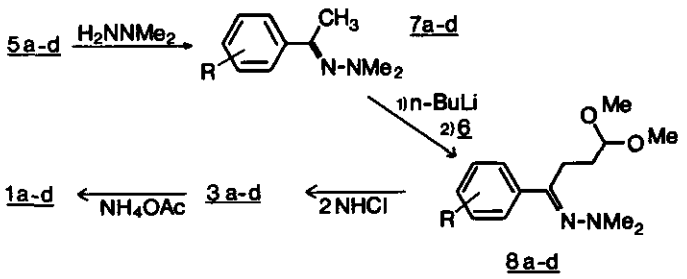
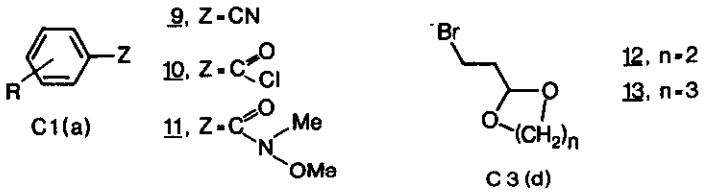


Table I. Synthesis of 2-phenylpyrroles 1 from acetophenones 5 (method I).

		yields,%[a]		
entry	R	5→7	7→8[b]	8→3→1
a	H	81	58(70)	67
b	4-F	91	59(70)	61
c	3-Cl	82	58(70)	58
d	2-OCH_3	80	71	52

[a]Yields were not optimized and refer to purified products after distillation (7,8) or crystallization (1) (see Experimental part); [b]yields in brackets are corrected for recovered 7 .

Method II, $C_1(a)+C_3(d)$ connection. Coupling of substituted benzoic acid derivatives 9, 10 or 11 as $C_1(a)$ reagents with commercially available cyclic bromoacetals 12 or 13 as $C_3(d)$ building blocks constitutes an attractive alternative for the formation of 3. Grignard reagents derived from 12 and 13 have been used in C_3-annelation reactions of enones[19] and arylaldehydes[20]. We initially studied the reaction of benzonitriles 9 with the more stable Grignard reagent from 13. The expected ketoacetals could be isolated in excellent yields (80-90%), but subsequent hydrolysis of the 1,3-dioxanyl moiety proceeded slowly and gave only low yields of 3.[21]



Since 2-monosubstituted 1,3-dioxolanes are known to hydrolyse faster than the corresponding 1,3-dioxanes[22], we next studied reagent 12. However, decomposition of the Grignard reagent from 12 was found to proceed faster than addition to the nitrile function and therefore the more electrophilic benzoyl chlorides 10 and N-methoxy-N-methylbenzamides 11 were used. To exclude the possibility of subsequent carbinol formation in the case of 10, the Cu(I)-Grignard complex of 12 was used in the coupling reaction.[23] Deprotection of the ensuing 2-(2-benzoylethyl)-1,3-dioxolanes 14 to 3 was most conveniently carried out by prolonged hydrolysis of the coupling-reaction mixture, giving 3 from 10 or 11 in a one-pot procedure. Subsequent ammonium acetate treatment resulted in 1 in quite acceptable overall yields (see Table II). In the case of reagents with one bulky ortho substituent (entries h and j) the coupling reactions proceeded sluggishly and the yields of the end-products 1h and 1j were somewhat lower.

Method II C1(a) + C3(d) fragments

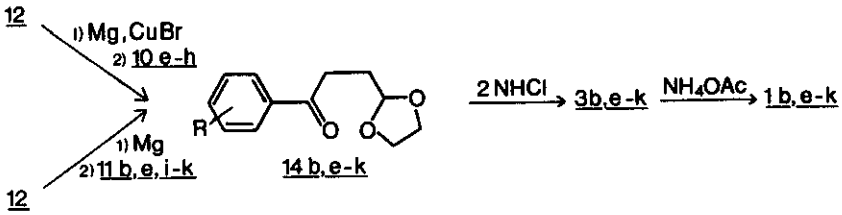
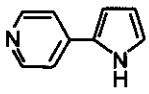


Table II. Synthesis of 2-phenylpyrroles 1 from benzoyl chlorides 10 and N-methoxy-N-methylbenzamides 11 (method II).

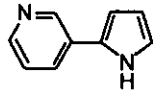
		yield,%[a,b]			yield,%[a,c]
entry	R	10 → 1	entry	R	11 → 1
e	4-CF_3	69	b	4-F	66
f	4-(i)C_3H_7	42	e	4-CF_3	45
g	2,6-diF	52	i	3-CF_3	67
h	2-OCH_3,5-$SO_2C_2H_5$	34	j	2-CF_3	22
			k	4-CN	40

[a]see footnote a, Table I; [b]overall yields for the sequence 10→14→3→1; [c]overall yields for the sequence 11→14→3→1.

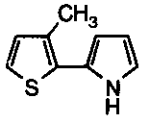
This method was successfully extended to heteroaryl substrates, giving 2-arylpyrroles 15-17 from the corresponding N-methoxy-N-methylamides in the indicated overall yields.



15, 39%

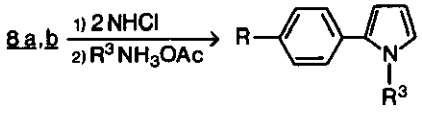


16, 43%



17, 55%

Synthesis of 1-substituted derivatives. A further application of intermediates 3 was found by the possibility to replace ammonium acetate by aromatic and aliphatic primary ammonium acetates in the cyclization step. Starting from precursors 8a,b both 1-phenyl (18) and 1-(n)propyl (19) substituted pyrroles were obtained in good yields.



	R	R^3	yield, %
18	H	Ph	57
19	F	n-Pr	62

Conclusion. Both methods I and II constitute highly practical synthetic routes to 2-phenylpyrroles 1 and their 1-substituted derivatives starting from commercially available reagents in a small number (three and two, respectively) of efficient reaction steps. A variety of electron donating and withdrawing substituents in the phenyl ring is allowed. Moreover, replacement of the 2-phenyl substituent by a heteroaromatic group with either *electron-deficient* (15, 16) *or electron-excessive* (17) *character is possible.*

The choice between the two methods will be directed by the accessibility of the corresponding acetophenones 5 or benzoyl chlorides 10, or by the compatibility of certain aryl-substituents with the reaction conditions. We recommend these methodologies also for large scale preparations.

EXPERIMENTAL

General. Melting points are uncorrected. ^{1}H-Nmr (pmr) and ^{13}C-nmr (cmr) spectra were taken in $CDCl_3$ solution on a Brucker WP-200 or AM-400 instrument; δ in ppm relative to internal tetramethylsilane, J in Hz. For chromatography Merck silica gel type 60 (size 70-230 mesh) was used. Elemental analysis of new pyrroles were performed at TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands. The results for 1b-1h, 1j, 1k and 17 are available as supplementary data. Drying of organic solvents was done with sodium sulfate, unless noted otherwise. Acetophenones 5 and acetals 6, 12 and 13 were used as commercial products. Acid chlorides 10 were either purchased or prepared from the corresponding carboxylic acids. N-methoxy-N-methylamides 11 were prepared from 10 according to Nahm and Weinreb.[23]

Method I (Table I). Procedures are given for entry b.

4-Fluoroacetophenone-N,N-dimethylhydrazone (7b). A mixture of 4-fluoroacetophenone (13.8 g, 0.1 Mol) and N,N-dimethylhydrazine (24.0 g, 0.4 Mol) in absolute ethanol (40 ml) was refluxed for 5 days. After removal of most of the ethanol, dichloromethane (100 ml) was added. The resulting solution was dried and evaporated to give a yellow oil. Distillation gave 16.4 g (91%) of pure 7b (bp 80.5°C,3.0 mm Hg). Pmr:δ 2.33 (s,3H,C-CH_3), 2.59 (s,6H,N(CH_3)$_2$), 7.04 (t,J=9Hz,2H,3,5-H), 7.72 (dd,J=6 and 9Hz,2H,2,6-H).

4-Dimethylhydrazono-4-(4-fluorophenyl)butanaldimethylacetal (8b). To a stirred solution of 7b (7.2 g, 0.040 Mol) in dry THF (75 ml), cooled at -70°C, was added slowly in a nitrogen atmosphere n-butyllithium (26 ml of a 1.55 M solution in hexane). The temperature was raised to -30°C and then bromoacetaldehyde dimethylacetal 6 (8.1 g, 0.048 Mol) in dry THF (50 ml) was added. Stirring was continued for 2 h at -25°C and then at room temperature during 16 h. After addition of water (100 ml) and extraction with ethyl acetate the organic layers were dried and concentrated. Distillation of the residue gave 6.3 g (59%) of pure 8b (bp 130-138°C,1.5 mm Hg), along with 0.8 g (11%) of 7b. Pmr: δ 1.69-180 (m,2H,C-CH_2-C), 2.54

(s,6H,N(CH_3)$_2$, 2.88-2.95 (m,2H,N=C-CH_2), 3.32 (s,6H,(OCH_3)$_2$, 4.37 (t,J=6Hz,1H,C-CH), 7.06 (t,J=9Hz,2H,3,5-arom. H), 7.67 (dd,J=6 and 9Hz,2H,2,6-arom. H).

4-(4-Fluorophenyl)-4-oxobutanal (3b). To a chilled solution of 8b (2.68 g, 0.01 M) in THF (10 ml) was added 2N HCl (20 ml). After stirring at room temperature for 1 h the reaction mixture was extracted with dichloromethane (3x30 ml) and dried. Removal of the solvents gave crude 3b 1.55 g(86%) which was used in the next step without further purification. TLC: Rf=0.22 (ether-petroleum ether/1-1).

2-(4-Fluorophenyl)pyrrole (1b). A mixture of 3b (1.55 g) and ammonium acetate (6.2 g, 8.0 equiv.) in ethanol (25 ml) was refluxed for 1.5 h. After removal of most of the ethanol in vacuo, a 5% solution of sodium bicarbonate in water (100 ml) was added. The mixture was extracted with dichloromethane (3x40 ml). The combined dichloromethane extracts were dried and evaporated in vacuo. After crystallization from cyclohexane pure 1b 0.98 g (71%) was obtained.

Method II (Table II). Procedures starting with benzoyl chlorides 10 and N-methoxy-N-methylbenzamides 11 are given for entry e and b, respectively.

2-[2-(4-Trifluoromethylbenzoyl)ethyl]-1,3-dioxolane (14e) and 4-Oxo-4-(4-trifluoromethylphenyl)butanal (3e). A mixture of magnesium (4.9 g, 0.20 Mol) and dry THF (100 ml) was stirred in a nitrogen atmosphere. Then was added dropwise a solution of 12 (25.0 g, 0.14 Mol) in THF (200 ml), maintaining the temperature at 25-30°C [19a]. After 30 min the solution was transferred under nitrogen into another flask (to remove excess of magnesium). After cooling at 0°C cuprous bromide (18.6 g, 0.13 Mol) was added. After stirring for 15 min at 5°C, the purple solution was cooled to -70°C and a solution of 10e (22.9 g, 0.11 Mol) in dry THF (100 ml) was added dropwise in 30 min. The reaction mixture was stirred at -70°C for 30 min and then allowed to warm up to 15°C. After stirring at 15°C for 1 h the mixture was cooled at 0°C and quenched with 2N HCl (350 ml).

Isolation of 14e. Immediate extraction with ether (3x100 ml) and washing the combined ether extracts with water (2x100 ml) and brine and drying over sodium sulphate-sodium carbonate gave 14e after evaporation of the solvent: 21.8 g (72%). After chromatography (eluent dichloromethane) a pure sample was obtained; mp 73-74°C. Pmr: δ 2.12-2.22 (m,2H,C-CH_2-C), 3.15 (t,J=7Hz,2H,O=C-CH_2-C), 3.83-4.10 (m,4H,O-CH_2-CH_2-O), 5.01 (t,J=9Hz,1H,C-CH), 7.73 (d,J=8Hz,2H,3,5-arom.H), 8.08 (d,J=8Hz,2H,2,6-arom.H).

Direct Conversion to 3e. After addition of 2N HCl stirring was continued for 16h. Work-up as described above gave 3e 20.2 g (80%), which was used in the next step without further purification. A pure sample of mp 41-43°C was obtained by chromatography (eluent dichloromethane). Pmr: δ 2.84 (t,J=6Hz,2H,2-CH_2), 2.98 (t,J=6Hz,2H,3-CH_2), 7.72 (d,J=8Hz,2H,3,5-arom.H), 8.10 (d,J=8Hz,2H,2,6-arom.H), 9.91 (s,1H,CHO).

2-(4-Trifluoromethylphenyl)pyrrole (1e). By reaction of 3e (10.8 g, 0.047 M) with ammonium acetate, using the procedure described above for the conversion of 3b into 1b, pyrrole 1e was isolated and purified by chromatography (eluent dichloromethane) and crystallization from cyclohexane: 8.5 g (86%).

2-(4-Fluorophenyl)pyrrole (1b) from 11b. To the Grignard reagent prepared from 12 (13.6 g, 0.075 Mol) as described above was added a solution of 11b[23] (9.15 g, 0.050 Mol) in THF (50 ml). After stirring at 20°C for 1 h the chilled reaction mixture was quenched with 1N HCl (75 ml). After extraction with ether, the combined organic layers were washed with water (2x50 ml) and dried. Evaporation of the solvents yielded crude 14b, which was first converted into 3b by treatment with 2N HCl and then into 1b by reaction with ammonium acetate, following the procedures described above. Purification by chromatography (eluent ether-petroleum ether/1-1) and crystallization gave pure 1b in the yield indicated in Table II.

Physical and spectroscopic properties of 2-phenylpyrroles 1a-1k are presented in Table III.

2-(4-Pyridyl)pyrrole (15). Mp 172-173°C; lit.[25] 175°C; pmr: δ 6.35 (m,1H,4-H), 6.76 (m,1H,3-H), 6.97 (m,1H,5-H), 7.38 (d,2H,2',6'-H), 8.52 (d,2H,3',5'-H), 9.55 (bs,1H,1-H); for J in pyrrole see Table III, note b.

2-(3-Pyridyl)pyrrole (16). Mp 98-99°C; lit.[25] 102°C; pmr: δ 6.32 (m,1H,4-H), 6.59 (m,1H,3-H), 6.91 (m,1H,5-H), 7.24 (m,1H,5'-H), 7.78 (m,1H,6'-H), 8.38 (dd,1H,4'-H), 8.80 (dd,1H,2'-H), 9.9 (br s,1H,1-H).

2-(3-Methyl-2-thienyl)pyrrole (17). Mp 39-40°C; pmr: δ 2.34 (s,3H,CH_3), 6.29 (m,1H,4-H), 6.34 (m,1H,3-H), 6.81 (m,1H,5-H), 6.88 (d,1H,4'-H), 7.08 (d,1H,5'-H), 8.2 (br s,1H,1-H).

Anal. Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58; S, 19.64. Found: C, 66.40; H, 5.65; N, 8.52; S, 19.74.

1,2-Diphenylpyrrole (18). To a solution of 3a (1.48 g, 9.1 mMol) in absolute ethanol (20 ml) was added aniline (0.84 ml, 9.2. mMol) and acetic acid (0.53 ml). After refluxing for 4 h, the solvent was removed and the residue was purified by chromatography (eluent: petroleum ether-ether/3-1) yielding 1.15 g 18 (57%); mp 82-83°C ; lit.[26] mp 92°C; cmr: δ 109.3 (3-C), 110.7 (4-C), 124.4 (5-C), 133.2 (2-C), 140.6 (N-C_6H_5,1'-C), 125.7-133.0 (arom.-C).

2-(4-Fluorophenyl)-1-(n-propyl)pyrrole (19). To a solution of 3b (3.78 g, 0.021 Mol) in ethanol (75 ml) was added n-propylamine (1.77 ml, 0.021 Mol) and acetic acid (1.2 ml). After refluxing for 1.5 h, the solvent was removed and the residue was purified by chromatography (eluent: petroleum ether-ether/95-5). Yield 2.66 g of 19 (62%); oil; cmr: δ 11.1 (CH_3), 34.8 (C-CH_2-C), 48.8 (N-CH_2), 122.0 (5-C), 108.9 (4-C), 107.8 (3-C), 133.2 (2-C); 136.1, 130.7, 115.3 and 163.0 (2-C_6H_4F;1'-C,2'-C,3'-C and 4'-C, respectively).

Table III. Physical and spectroscopic properties of 2-phenylpyrroles 1

Compound	R	m p (°C)	formula[a]	PMR data (δ, $CDCl_3$)[b] 1-H	3-H	4-H	5-H	R-H
1a	H	125-127[c]	-	8.45	6.52	6.30	6.84	7.46(2',6'-H),7.34(3',5'-H),7.19(4'-H)
1b	4'-F	123-124	$C_{10}H_8FN$	8.28	6.45	6.38	6.80	7.38(2',6'-H),7.03(3',5'-H)
1c	3'-Cl	79-80	$C_{10}H_8ClN$	8.34	6.53	6.29	6.82	7.40(2'-H),7.14(4'-H)7.18 and 7.32(5',6'-H)
1d	2'-OCH_3	66-67	$C_{11}H_{11}NO$	9.75[d]	6.61	6.27	6.80	6.87(3'-H),7.10(4'-H),6.95(5'-H),7.63(6'-H)
1e	4'-CF_3	161-162	$C_{11}H_8F_3N$	8.49	6.62	6.33	6.91	7.60(2',6'-H),7.53(3',5'-H)
1f	4'-i-C_3H_7	110-111	$C_{13}H_{15}N$	8.34	6.47	6.28	6.80	7.38(2',6'-H),7.20(3',5'-H)
1g	2',6'-diF	oil[e]	$C_{10}H_7F_2N$	9.12	6.88	6.34	6.91	6.90-7.05(3',4',5'-H)
1h	2'-OCH_3,5'-$SO_2C_2H_5$	130-133	$C_{13}H_{15}NO_3S.$ 0.25 AcOAc	9.75[d]	6.73	6.31	6.90	7.07(3'-H),7.66(4'-H),8.12(6'-H)
1i	3'-CF_3	84-85[f]	-	8.45	6.59	6.32	6.89	7.67(2'-H),7.60(4'-H),7.44(5'-H),7.42(6'-H)
1j	2'-CF_3	70	$C_{11}H_8F_3N$	8.48	6.42	6.31	6.91	7.72(3'-H),7.37(4'-H),7.50(5',6'-H)
1k	4'-CN	109-110	$C_{11}H_8N_2$[g]	8.8	6.67	6.34	6.95	7.53(2',6'-H),7.60(3',5'-H)

[a] Satisfactory analyses (C, H, N, Cl, F, S; ±0.4%) were obtained; [b] Coupling constants (J in Hz, ±0.02): H-13, H-14 and H-15, 2.7; H-34, 3.7; H-35, 1.5; H-45, 2.6; [c] Lit.[20] m p 126°C and lit.[3] m p 129°C; [d] Downfield shift due to H-bridge with 2'-OCH_3; [e] n_D^{20}=1.5978; [f] Lit.[24] m p 84-85°C; [g] C, calcd:78.55; found:78.04.

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Received, 6th July, 1987