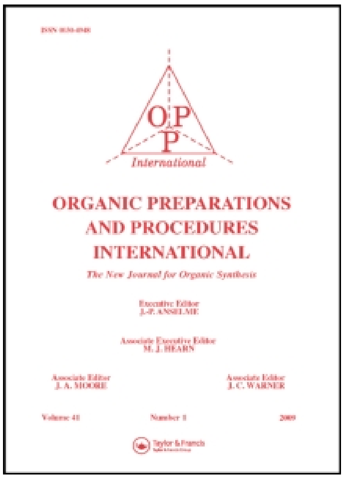

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A SIMPLE SYNTHESIS OF 3-(1-PYRROLYL) FLAVONOIDS

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evaporated *in vacuo* to give 0.47 g (98%) of VIIIb as colorless plates (EtOH), mp. 61.5-63°. ^{1}H-NMR ($CDCl_3$): δ 1.28 (18H, s), 1.70-2.04 (2H, m), 2.68 (4H, m), 3.76 (6H, s), 6.68-6.77 (2H, m), 7.07-7.16 (4H, m).

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85

Found: C, 81.44; H, 9.77

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A SIMPLE SYNTHESIS OF 3-(1-PYRROLYL) FLAVONOIDS

Submitted by (03/24/86)

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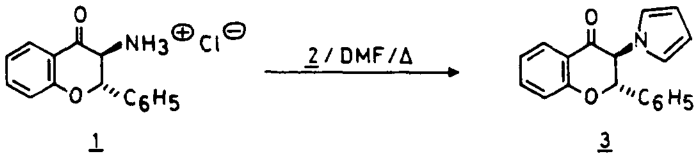
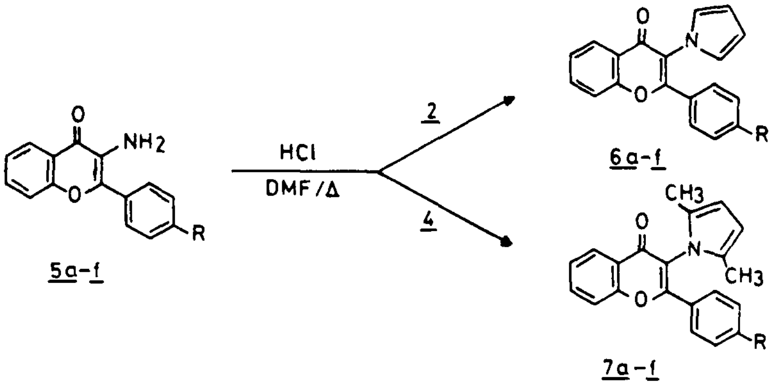
Several new routes for the synthesis of 3-aminoflavanones and flavones and their N-alkylated derivatives developed earlier,[1-5] failed to afford 3-azolylflavonoids because of the low nucleophilicity of the azole system. Recently, a modified method[6,7] reported for the preparation of 1H-pyrroles prompted us to utilize this reaction for the synthesis of the hitherto unknown 3-(1-pyrrolyl)flavanones (3) and flavones (6 and 7).

The reaction of trans-3-aminoflavanone hydrochloride (1) with 2,5-dimethoxytetrahydrofuran (2) in hot N,N-dimethylformamide resulted in the expected trans-3-(1-pyrrolyl)flavanone (3), but attempts to prepare 3-(2,5-dimethyl-1-pyrrolyl)flavanone, using 2,5-hexanedione (4) instead of acetal 2, were unsuccessful. Treatment of 3-aminoflavones (5a-f) with acetal 2 or dione 4 in the presence of additional hydrogen chloride afforded the corresponding 3-(1-pyrrolyl)flavones (7a-f), respectively. Without hydrogen chloride, no reaction was observed.





a) R = H b) R = Me c) R = MeO d) R = F e) R = Cl f) R = Br

EXPERIMENTAL SECTION

Melting points were measured on a Kofler hot-stage and are uncorrected. IR spectra were recorded with a Perkin-Elmer 283 instrument as KBr discs. ^{1}H-NMR spectra were obtained on a Bruker WP 200 SY (200 MHz) spectrometer in $CDCl_3$ solutions using TMS as an internal standard. trans-3-Aminoflavanone hydrochloride (1) was prepared according to ref. 8 and 3-aminoflavones (5a-f) according to ref. 5.

trans-3-(1-Pyrrolyl)flavanone (3).- A solution of 2,5-dimethoxytetrahydrofuran (1.5 ml, 11.6 mmol) in dry dimethylformamide (10 ml) was added dropwise to a stirred solution of *trans*-3-aminoflavanone hydrochloride (1) (2.76 g, 10.1 mmol) in dry dimethylformamide (50 ml) over 10 min. at reflux. After 30 min. the mixture was poured into ice-cold 10% hydrochloric acid; the dark solid which separated was collected, dried and boiled with ethanol (40 ml). Recrystallization of the insoluble residue from a mixture of 1:2 ethanol-ethyl acetate gave 1.10 g (41%) 3 as colorless plates, mp. 222-224°.

TABLE 1. Physical Data of Flavones 6 and 7

Product	Yield[a] (%)	mp. (°C)	C=O (cm^{-1})	IR (cm^{-1}) Flavanone skeleton	C=C (pyrrole)
6a[b]	69	172-174	1640	1382,1310,1262,1285	1014(w)
6b	25	199-200	1641	1381(w),1309,1266	1018(w)
6c	21	212-214	1630	1382(w),1308,1255	1024
6d	23	201-203	1634	1383(w),1310,1265	1014
6e	33	192-194	1637	1383,1310,1265,1256	1011
6f	28	199-201	1645	1379(w),1308,1259	1009
7a[c]	63	137-139	1639	1373,1311,1268	1018,1009
7b	50	180-182	1641,1651(sh)	1372,1309,1272	1016,1007
7c	51	196-197	1642	1370,1309,1260	1023
7d	37	158-160	1656,1639	1370,1311,1270,1264	1023,1011
7e	51	165-166	1639,1656	1368,1311,1260	1025
7f	28	152-154	1639,1656	1367,1310,1260	1025,1008

a. Yields refer to recrystallized products. b. ^{1}H-NMR: δ 8.34 (dd,1H, H-5), 6.60 (d, 2H, H-2", 5"), 6.28 (d, 2H, H-3", 4"). c. ^{1}H-NMR: δ 8.29 (dd, 1H, H-5), 5.93 (s, 2H, H-3", 4"), 1.90 (s, 6H, 2", 5"-CH_3)

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84

Found: C, 78.62; H, 5.40; N, 4.79

IR: 1701 (C=O), 1320, 1290 (Ar-C=O)), 1224 (C-O-C), 1036, 1022 cm^{-1} (pyrrolyl); ^{1}H-NMR: δ 7.99 (dd, 1H, H-5), 6.38 (d, 2H, H-2", 5"), 6.05 (d, 2H, H-3", 4"), 5.55 (d, J = 12 Hz, 1H, H-2); 5.04 (d, J = 12 Hz, 1H, H-3).

3-(1-Pyrrolyl)- and 3-(2,5-dimethyl-1-pyrrolyl)-4'-R-flavones (6a-f, 7a-f). General Procedure.- To a stirred solution of 3-aminoflavone 5a-f (10 mmol) in dry dimethylformamide (60 ml) was added ethereal hydrogen chloride (saturated at 0°, 2.5 ml) then the mixture was heated to reflux and a solution of 2,5-dimethoxytetrahydrofuran (2) or 2,5-hexanedione (4) (12 mmol) was added dropwise over 10 min. After 30 min. stirring at this temperature, the mixture was poured into a mixture of crushed ice (200 g) and conc. hydrochloric acid (10 ml). The precipitate was collected, washed with water and recrystallized from ethanol affording pure 6 and 7, respectively. (See Tables 1 and 2).

TABLE 2. Analytical Data of Flavones 6 and 7

Product	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
6a	$C_{19}H_{13}NO_2$	79.43	4.56	4.88	79.38	4.50	4.79
6b	$C_{20}H_{15}NO_2$	79.72	5.02	4.65	79.64	5.11	4.63
6c	$C_{20}H_{15}NO_3$	75.70	4.76	4.41	75.79	4.67	4.29
6d	$C_{19}H_{12}FNO_2$	74.75	3.96	4.59	74.62	4.09	4.50
6e	$C_{19}H_{12}ClNO_2$	70.92	3.76	4.35	70.82	3.88	4.29
6f	$C_{19}H_{12}BrNO_2$	62.32	3.30	3.82	62.21	3.18	3.69
7a	$C_{21}H_{17}NO_2$	79.98	5.43	4.44	79.84	5.53	4.51
7b	$C_{22}H_{19}NO_2$	80.22	5.81	4.25	80.31	5.90	4.30
7c	$C_{22}H_{19}NO_3$	76.50	5.54	4.06	76.57	5.59	4.11
7d	$C_{21}H_{16}FNO_2$	75.66	4.84	4.20	75.59	4.71	4.11
7e	$C_{21}H_{16}ClNO_2$	72.10	4.61	4.00	72.19	4.49	3.85
7f	$C_{21}H_{16}BrNO_2$	63.97	3.07	3.55	64.06	3.02	3.45

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AN IMPROVED PREPARATION OF 1,2,5-TRIMETHYL-3-NITROPYRROLE. FRIEDEL-CRAFTS ACYLATION WITH 2-FLUOROBENZOYL CHLORIDE

Submitted by M. R. Pavia
(02/25/86)

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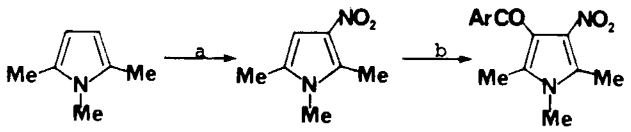
As part of our drug discovery effort, we required a facile synthesis of various substituted phenyl(1,2,5-trimethyl-4-nitropyrrol-3-yl)methanones (3). It is conceivable that compounds of type 3 could be prepared by Friedel-Crafts acylation of 1,2,5-trimethyl-3-nitropyrrole (2). The introduction of the various phenyl moieties in the last step would allow for the use of a common penultimate intermediate 2 and thus facilitate the preparation of a series of congeners.



1 2 3

a) H_2SO_4, 0° b) ArCOCl, $AlCl_3$, 50° Ar = o-FC_6H_4