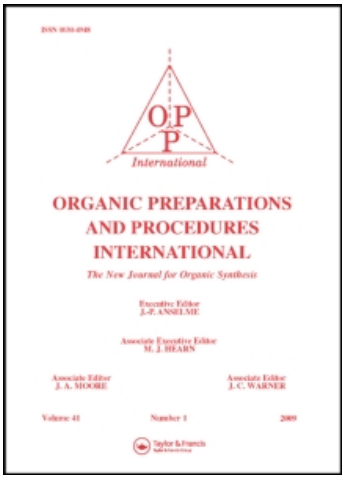


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF MANNICH COMPOUNDS FROM FLAVANONES

György Litkei[a]; Tamás Patonay[a]; Jenó Kardos[a]
[a] Department of Organic Chemistry, Kossuth Lajos, University, Debrecen, HUNGARY

To cite this Article Litkei, György , Patonay, Tamás and Kardos, Jenó(1990) 'SYNTHESIS OF MANNICH COMPOUNDS FROM FLAVANONES', Organic Preparations and Procedures International, 22: 1, 47 — 55
To link to this Article: DOI: 10.1080/00304949009356665
URL: http://dx.doi.org/10.1080/00304949009356665

ORGANIC PREPARATIONS AND PROCEDURES INT. 22(1), 47-56 (1990)

SYNTHESIS OF MANNICH COMPOUNDS FROM FLAVANONES

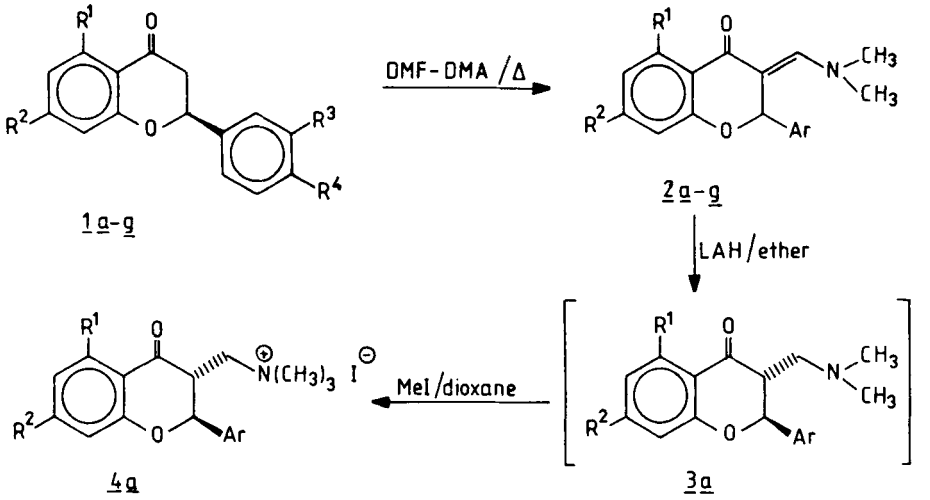
György Litkei*, Tamás Patonay and Jenő Kardos

Department of Organic Chemistry, Kossuth Lajos University H-4010 Debrecen, P. O. Box 20. HUNGARY

The synthesis of a series of chromanone and flavanone derivatives of considerable pharmacological activities has been achieved by the classic Mannich reaction.[1,2] Yields of these reactions are generally poor[1] and alkylation of the aromatic ring[3] may take place as well. Recently Schuda et al.[4] described an excellent method for the preparation of enaminones from active methylene compounds with amide acetals. This procedure proved to be suitable to synthesize enaminones (2) from flavanones (1) with dimethylformamide dimethyl acetal (DMF-DMA). This method affords enaminone (2) in higher yield than the previously published procedure[2] and the reaction is not considerably influenced by the substitution pattern of rings A and B of the flavanone (see Table 1).

The reduction of enaminone 2a with lithium aluminium hydride according to Martin et al.[5] afforded Mannich base 3a which was isolated as quaternary salt (4a), reducting of the carbonyl group was not observed in these conditions. This is presumably due to the formation of the unreactive[5] cyclic complex (5).

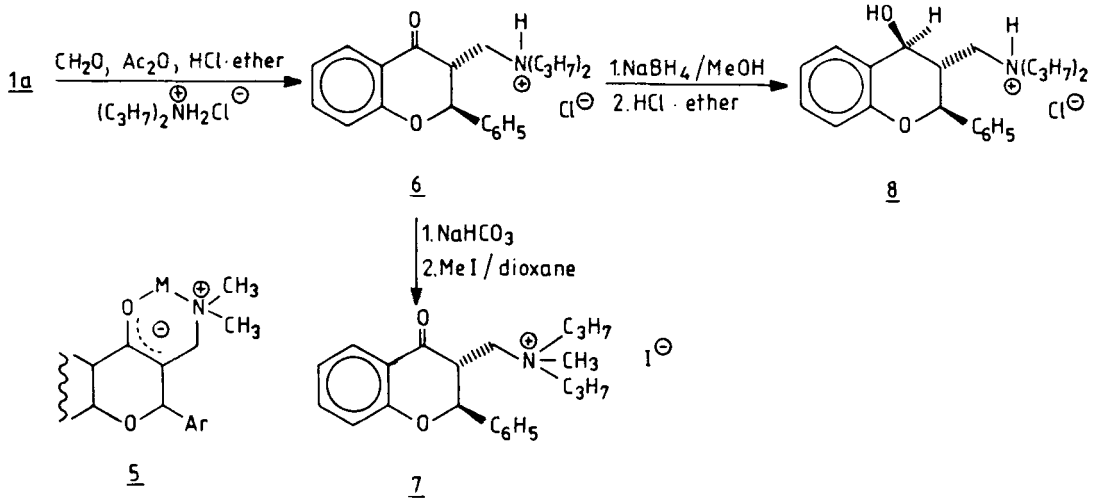
Flavanone 1a was converted into Mannich product 3a utilizing the modified procedure of Sircar et al.[6] by the reaction



1a-g 2a-g 3a 4a

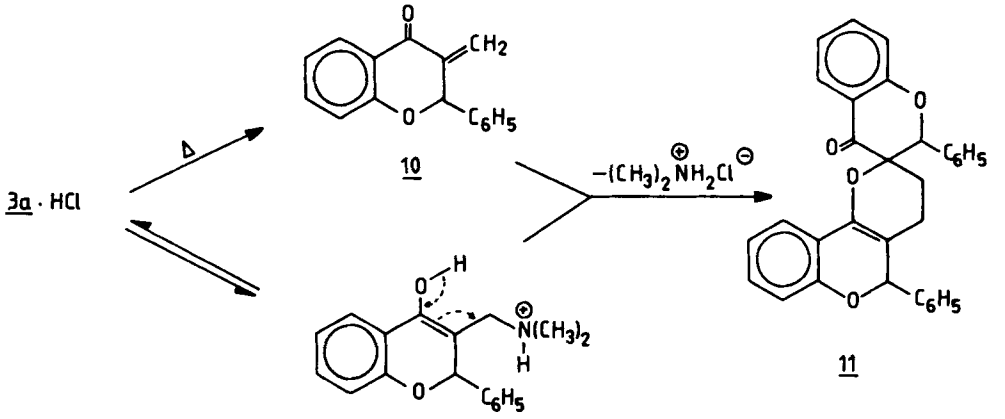
a, R^1-R^4=H; b, R^1=OCH_3; R^2-R^4=H; c, R^2=OCH_3; R^1,R^3,R^4=H;
d, R^2=$OCH_2C_6H_5$; R^1,R^3,R^4=H; e, R^2=Cl; R^1,R^3,R^4=H;
f, R^1,R^2=H; R^3,R^4=$O(CH_2)_2O$; g, R^1,R^2=H; R^3,R^4=$O(CH_2)_3O$

of formaldehyde and dimethylamine hydrochloride in the presence of acetic anhydride and ethereal hydrogen chloride. Reaction of 3a with methyl iodide in dioxane yielded quaternary salt 4a. The hydrochloride of the 3-[(dipropylamino)methyl]-flavanone (6) and quaternary salt 7 from the base were prepared with dipropylamine hydrochloride using the above-mentioned procedure.



6 8 5 7

The substance obtained by the reduction of 6 with sodium borohydride was prepared as hydrochloride and it proved to be 2,3--trans-3,4-trans-isomer (8) according to its ^{1}H-NMR spectrum. In the absence of ethereal hydrogen chloride, the product of the Mannich reaction was not 3a but the dimer 11, whose structure was established by spectral data (^{1}H-, ^{13}C-NMR and MS).



In accordance with literature data,[7] decomposition of 3a. HCl leads to 3-methyleneflavanone (10) which reacts with the enol form of compound 9 to afford 11 which was also obtained by refluxing an aqueous solution of 3a.HCl for 2 hrs. The investigation on the stereochemictry of 11 is in progress.

EXPERIMENTAL SECTION

Melting points were measured on a Kofler hot-stage and are uncorrected. IR spectra were recorded with a Perkin-Elmer 283 instrument in KBr discs. ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker WP 200 SY spectrometer in $CDCl_3$ solution unless otherwise stated. TMS was used as internal standard. Mass spectra were recorded with a VG 7035 GC-MS system, electron impact at 70 eV.

3-[(Dimethylamino)methylene]flavanones (2a-g). General Procedure.- Flavanone (1a-g, 10 mmol)[8-10] and dimethylformamide dimethyl acetal (DMF-DMA) (40 mmol) were allowed to react to 110° and the reaction was monitored by TLC (DC-Alurolle, Kieselgel 60 F_{254}; benzene:methanol 15:1). After the disappearance of the flavanone, the solvent was evaporated under reduced pressure and the residue crystallized from anhydrous ethanol (Tables 1 and 2).

3-[(Trimethylammonio)methyl]flavanone iodide (4a).- a) A solution of 2a (5.3 mmol) in anhydrous ether (300 mL) was added rapidly (approx. 5-10 min) to a vigorously stirred ice-cold suspension of lithium aluminum hydride (5.9 mmol) in anhydrous ether (20 mL). The mixture was stirred for 10 min, then quenched with ethyl acetate and water. The solution was dried, the solvent evaporated, and the oily residue was allowed to react with methyl iodide (5 mL) dissolved in dioxane (25 mL) at room temperature for 24 hrs. The precipitate was collected, washed with anhydrous ether to yield 47% of 4a as white crystals, mp. 180--182°. b) A mixture of dimethylamine hydrochloride (12 mmol), anhydrous ether (25 ml), 37% formaldehyde (2 mL), and ethereal hydrogen chloride (5 mL) was stirred at 0° for 1 h, then 10 mmol of flavanone (1a) dissolved in acetic anhydride (30 mL) was added in drops. This mixture was refluxed for 10 hrs then the solvent evaporated. The solid residue was stirred with a mixture of sodium hydrogen carbonate solution and chloroform under cooling. The organic layer was separated, washed and dried, then the solvent evaporated. The residue was dissolved in dioxane (20 ml) and allowed to react with methyl iodide (15 mL) on a hot steam-bath for 2 hrs. The precipitate was filtered off,

washed with anhydrous ether to afford 54% 4a, mp. 180-182°.

Anal. Calcd. for $C_{19}H_{22}INO_2$: C, 55.18; H, 5.09; I, 29.15; N, 3.21

Found: C, 55.21; H, 5.10; I, 29.45; N, 3.25

IR : 2826 [$2\delta_s CH_3$, $\overset{\oplus}{N}(CH_3)_3$], 1690 (C=0), 1605, 1472, 1462 (CC), 1310 (Ar-C(=0)), 1221, 1210 w, 1148, 995 (Flavanone skeleton) cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ7.88 (dd, 1H, H-5), 5.71 (d, 1H, H-2; J=12 Hz), 4.25, 3.95 (ABX, 2x1H, $CH_2\overset{\oplus}{N}$; J_{AB}=13 Hz), 2.8 (10 H, 3xCH_3 + H3) ppm.

3-[(Dipropylamino)methyl]flavanone hydrochloride (6).- The reaction was performed according to Method b, using dipropylamine hydrochloride instead of dimethylamine hydrochloride. After 10 hrs reflux the solvent was evaporated and the residue triturated with anhydrous ether. The solid material was filtered off, crystallized from a mixture of anhydrous ethanol-hexane (1:1) to obtain 59% of 6, mp. 196-198°.

Anal. Calcd. for $C_{22}H_{28}ClNO_2$: C, 70.66; H, 7.54; Cl, 9.48; N, 3.74

Found: C, 70.49; H. 7.53; Cl, 9.50; N, 4.01

IR : 2960 ($\nu_{as}CH_3$), 2930 ($\nu_{as}CH_2$), 2872 ($\nu_s CH_3$), 2570, 2430 ($\overset{\oplus}{N}$H), 1690 (C=0), 1604, 1575 (CC), 1321, 1308, 1293 (Ar-C(=0)), 1226, 985 (Flavanone skeleton) cm^{-1}. ^{1}H NMR (DMSO-d_6) : δ10.31 (br, 1H, $\overset{\oplus}{N}$H), 5.68 (d, 1H, H-2; J=11.5 Hz), 4.15, 3.65 (ABX, 2x1H, $CH_2\overset{\oplus}{N}$; J_{AB}=12 Hz), 2.8 (m, 5H, $N\overset{\oplus}{C}H_2CH_2CH_3$ + H-3), 1.1-1.6 (m, 4H, $NCH_2CH_2CH_3$), 0.80, 0.73 (2xt, 2x3H, $NCH_2CH_2CH_3$) ppm.

3-[(Methyldipropylammonio)methyl]flavanone iodide (7).- Five mmol of 6 was stirred with a cold mixture of sodium hydrogen carbonate (10 mL) and chloroform (10 mL), then separated. The organic layer was washed with water, dried and the solvent evapo-

TABLE 1. Data of Flavanones 2a-g

Comp.	Time (hrs)	Yield[a] (%)	mp. (°C)	Calcd. (Found) C	H	N
2a	8	45	165-167[b]	77.39 (77.42)	6.13 (6.20)	5.01 (4.93)
2b	2.5	40	182-184	73.76 (73.54)	6.19 (6.21)	4.53 (4.58)
2c	6	45	179-181	73.76 (73.82)	6.19 (6.10)	4.53 (4.57)
2d	4	65	154-156	77.90 (77.83)	6.01 (6.18)	3.63 (3.57)
2e	2.5	70	190-192	68.89 (68.76)	5.14 (5.02)	4.46 (4.37)
2f	2.5	70	178-180	71.20 (71.18)	5.67 (5.42)	4.15 (4.08)
2g	2.5	70	197-199	71.77 (71.72)	6.02 (6.10)	3.98 (3.97)

a, Yields refer to the recrystallized products.

b, Lit.[2] mp. 167°.

TABLE 2. Spectral Data of Flavanones 2a-g

Comp.	IR (cm^{-1}) νC=O	νC=C	^{1}H NMR (δ) H-2	=CHN	$N(CH_3)_2$	Others
2a	1646	1550	6.65s	7.80s	3.02s	-
2b	1649	1556	6.67s	7.81s	3.05s	3.67s ($OC\underline{H}_3$)
2c	1650	1551	6.63s	7.83s	3.04s	3.83s ($OC\underline{H}_3$)
2d	1648	1548	6.67s	7.83s	3.04s	4.98s ($C\underline{H}_2$)
2e	1642	1542	6.69s	7.87s	3.05s	-
2f	1648	1547	6.57s	7.83s	3.08s	4.19s ($OC\underline{H}_2C\underline{H}_2O$)
2g	1642	1550	6.57s	7.82s	3.08s	2.14m ($OCH_2C\underline{H}_2CH_2O$) 4.14m ($OC\underline{H}_2CH_2C\underline{H}_2O$)

rated. The oily residue was dissolved in dioxane (15 mL) and

rated. The oily residue was dissolved in dioxane (15 mL) and allowed to react with methyl iodide (10 mL) at room temperature for 24 hrs. The precipitate was filtered off, washed with anhydrous ether to yield 65% of 7, mp. 202-204°.

Anal. Calcd. for $C_{23}H_{30}INO_2$: C, 57.62; H, 6.30; I, 26.47; N, 2.92

Found: C, 57.48; H, 6.22; I, 26.24; N, 2.97

IR : 2964 ($\nu_{as}CH_3$), 2862 ($\nu_s CH_3$), 2833 ($2\delta_s CH_3$, $\overset{\oplus}{N}Me_3$), 1687 (C=O), 1608, 1581 w (CC), 1307 (Ar-C(=O)), 1233, 1148 (Flavanone skeleton) cm^{-1}. ^{1}H NMR (DMSO-d_6) : δ 7.88 (dd, 1H, H-5), 5.72 (d, 1H, H-2, J=11.5 Hz), 4.31, 3.96 (ABX, 2x1H, $C\underline{H}_2\overset{\oplus}{N}$; J_{AB}=12.5 Hz), 3.0 (m,~5H, $\overset{\oplus}{N}C\underline{H}_2CH_2CH_3$ + H-3), 2.69 (s, 3H, $\overset{\oplus}{N}C\underline{H}_3$), 1.65, 1.42 (2xm, 2x2H), $\overset{\oplus}{N}CH_2C\underline{H}_2CH_3$), 0.85, 0.65 (2xt, 2x3H, $\overset{\oplus}{N}CH_2CH_2CH_3$) ppm.

2,3-trans-3,4-trans-3-[(N,N-dipropylamino)methyl]-4-hydroxyflavan hydrochloride (8).- To 2.5 mmol of 6 dissolved in hot anhydrous methanol (25 mL), sodium borohydride (1.0 g) was added in small portions. The mixture was refluxed for 2 hrs, poured into water and extracted with ether. The ethereal solution was washed, dried, and the solvent evaporated. The residue was dissolved in ether (20 mL) and ethereal hydrogen chloride (10 mL) was added. The precipitate was filtered off to afford 95% of 8, mp. 215-127°.

Anal. Calcd. for $C_{22}H_{30}ClNO_2$: C, 70.28; H, 8.08; Cl, 9.43; N, 3.72

Found: C, 70.14; H, 8.12; Cl, 9.54; N, 3.82

IR : 3250 (OH), 2962 ($\nu_{as}CH_3$), 2928 ($\nu_{as}CH_2$), 2600 ($\nu\overset{\oplus}{N}H$), 1227, 1038 (Flavane skeleton) cm^{-1}. ^{1}H NMR (DMSO-d_6) : δ 9.26 (s, 1H, $\overset{\oplus}{N}\underline{H}$), 5.15 (d, H-2; J_{23}=10 Hz), 5.03 (d, H-4), 2,9 (m, 6H, $C\underline{H}_2\overset{\oplus}{N}H$ $(C\underline{H}_2CH_2CH_3)_2$, 1.68, 1.38, 1.18 (m, 2x2H, $\overset{\oplus}{N}H$ $(CH_2C\underline{H}_2CH_3)_2$, 0.85, 0.74 (2xt, 2x3H, $C\underline{H}_3$) ppm. ^{1}H NMR (D_2O) : δ 5.15 (d, H-2; J_{23}= 10 Hz), 5.05 (d, H-4; J_{34}=10 Hz), 3.39 (dd, H-3), 3 (m, 6H, $C\underline{H}_2\overset{\oplus}{N}H(C\underline{H}_2)_2$, 1.70, 1.15, 1.05 (m, 2x2H, $\overset{\oplus}{N}HCH_2C\underline{H}_2CH_3$), 0.85, 0.75 (2xt, 2x3H, $C\underline{H}_3$) ppm.

Preparation of 11.- Dimethylamine hydrochloride (12 mmol) was added to 37% formaldehyde (2 mL) and the mixture was allowed to stand at ambient temperature for 1 h. 10 mmol of flavanone (1a) dissolved in acetic anhydride (30 mL) was added and it was heated for 10 hrs. The solvent was evaporated and the residue triturated with anhydrous ether (20 mL) to yield 30% of 11, mp. 196-198°.

Anal. Calcd. for $C_{32}H_{24}O_4$: C, 81.33; H, 5.11
Found: C, 81.42; H, 5.23

IR : 1728, 1685 (C=O), 1649 (C=C), 1611, 1597, 1558, 1540, 1464 (CC), 1380, 1370, 1320, 1240, 1230, 1215, 1160 (Flavanone and flavene skeleton + νC-O-C). ^{1}H NMR ($CDCl_3$) : δ 7.99 (dd, 1H), 6.80-7.60 (16 H), 6.60 (dd, 1H), 5.70 (s, 1H), 5.53 (s, 1H), 2.07-1.82 (2xm, 2x1H), 1.59 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6) : C=O (191.70), quaterner C (159.82, 152.36, 141.12, 138,71, 133.67, 118.02, 117.92, 101.90), spiro C (78.22), aromatic CH (135.72, 128.45, 128.11, 127.96, 127. 69, 127.40, 121.76, 120.27, 120.11, 117.19, 115.05), OCH (83.11, 80.75), CH_2 (19.72, 18.13).
MS : 472 (M^+, 5.5), 471 (2.5), 434 (1), 395 (2.5), 352 (1.5),

351 (3), 276 (3.5), 261 (6), 249 (44), 248 (15), 247 (25), 235 (79.5), 223 (21), 207 (9.5), 189 (5), 181 (5), 178 (8), 172 (10), 159 (17), 151 (6), 147 (5), 131 (8), 128 (7.5), 121 (85), 115 (49.5), 92 (20.5), 91 (13), 89 (8), 65 (20.5), 63 (28), 49 (100).

REFERENCES

1. G. M. Cingolani, F. Gualtieri and M. Pigini, Farmaco Ed. Sci., 26, 718 (1971); W. Werner, Arch. Pharm., 309, 1011 (1976); A. Cascaval, Synthesis, 277 (1984).
2. F. E. Ward, D. L. Garling and R. T. Buckler, J. Med. Chem., 24, 1073 (1981).
3. V. Tychopoulos and J. H. P. Tyman, Synt. Commun., 16, 1401 (1986).
4. P. F. Schuda, C. B. Ebner and T. M. Morgan, Tetrahedron Letters, 27, 2567 (1986).
5. J. C. Martin, K. R. Barton, P. G. Gott and R. H. Meen, J. Org. Chem., 31, 943 (1966).
6. J. Sircar, B. L. Duell, M. H. Cain, S. E. Burke and J. A. Bristol, J. Med. Chem., 29, 2142 (1986).
7. D. F. Rane, A. G. Fishman and R. E. Pike, Synthesis, 694 (1984).
8. T. Patonay, Gy. Litkei, M. Zsuga and A. Kiss, Org. Prep. Proced. Int., 16, 315 (1984).
9. Gy. Litkei, T. Patonay, R. Bognár, V. Khilja, A. Aitmambetov, A. Turov and F. Babichev, Pharmazie, 39, 741 (1984).
10. T. Patonay, Gy. Litkei, E. Péli, V. P. Khilja and A. Aitmambetov, Pharmazie, 42, 662 (1987).

(Received April 13, 1989; in revised form July 10, 1989)