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SYNTHESIS OF SPIROCYCLOPROPANE CARBOXYLIC ACIDS FROM FLAVANONES AND THEIR CONVERSION TO THE CORRESPONDING PYRIDAZINONES

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The conversion of flavanones to spirocyclopropane carboxylic acids is reported. It has been shown that a mixture of three isomers is formed. Their structure and configuration have been elucidated from PMR data. Substituted pyridazinones were obtained from the synthesized acids.

3(2H)-Pyridazinones are finding an ever increasing use in medicinal chemistry as positive ionotropes [1-3] due to their structural association with non-steroidal and non-catecholamine cardiotonc agents. Quite recently the synthesis of 3(2H)-pyridazinones from tetralones [4, 5] and chromanones [5] has been reported. This stimulated our study of the synthesis of these compounds from flavanone and we have recently reported the synthesis of Ia, b [6]. In agreement with published data [5] these substances can be used to prepare spirocyclopropane carboxylic acids. In fact, flavanone Ia was converted to the

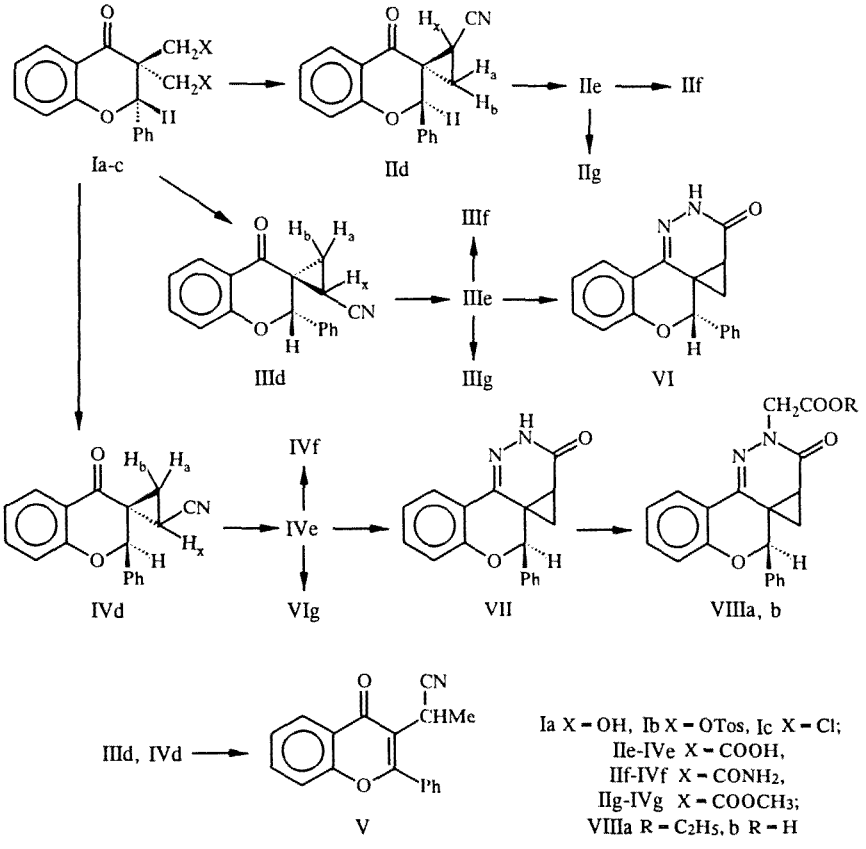

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TABLE 1. Physicochemical Properties of the Compounds Synthesized

Compound	Empirical formula	Mp, °C (solvent)	IR spectrum (KBr), ν, cm^{-1}	PMR spectrum, δ, ppm ($CDCl_3$)	Mass spectrum, m/z, %	Yield, %
1	2	3	4	5	6	7
IId	$C_{18}H_{13}NO_2$ (275,29)	166...168 (EtOH)	2240 (C≡N), 1686 (C=O)	1,47, 2,1, 2,56 (3H, d.d.), 5,6 (s, 2-H), 6,9...7,8 (9H, m, arH)	275 (40), 274 (8), 247 (5), 222 (100), 194 (15), 155 (16), 120 (75), 104 (55)	37
IIId	$C_{18}H_{13}NO_2$ (275,29)	192...194 (EtOH)	2246 (C≡N), 1688 (C=O)	0,98, 1,70, 2,23 (3H, d.d.), 5,80 (s, 2-H), 7,1...8,1 (9H, m, arH	275 (40), 247 (5), 222 (100), 194 (15), 155 (10), 120 (65), 104 (95)	12
IVd	$C_{18}H_{13}NO_2$ (275,29)	178...180 (EtOH)	2236 (C≡N), 1680 (C=O)	1,45, 190, 2,19 (3H, d.d.), 5,40 (s, 2-H), 7,0...8,0 (9H, m, arH)	275 (40), 274 (8), 247 (7), 222 (100), 194 (12), 155 (10), 120 (65), 104 (85)	38
IIe	$C_{18}H_{14}O_4$ (294,30)	182...184 ($CHCl_3$,hexane)	3422...3064 (OH), 1698 (COOH), 1680 (C=O)	1,65, 2,17, 2,59 (3H, d.d.), 5,95 (s, 2-H), 6,9...7,8 (9H, m, arH), 9,6 (1H, COOH)	294 (20), 293 (60), 277 (20), 276 (16), 249 (20), 247 (90), 221 (30), 121 (100), 104 (80)	38
IIIe	$C_{18}H_{14}O_4$ (294,30)	191...193 ($CHCl_3$)	3398...3064 (OH), 1714 (COOH), 1686 (C=O)	1,14, 2,08, 2,16 (3H, d.d.), 5,60 (s, 2-H), 7,0...7,9 (9H, m, arH), 9,35 (1H, COOH)	294 (30), 293 (1), 277 (6), 276 (7), 249 (60), 247 (10), 221 (20), 121 (80), 104 (100)	72
IVe	$C_{18}H_{14}O_4$ (294,30)	196...198 ($CHCl_3$)	3200...2500 (OH), 1710 (COOH), 1686 (C=O)	1,55*, 2,22, 2,56 (3H, d.d), 5,49 (s, 2-H), 7,0...7,6 (9H, m, arH), 12,2 (1H, COOH)	294 (22), 293 (7), 277 (5), 276 (6), 249 (60), 247 (20), 221 (23), 121 (82), 104 (100)	85
IIf	$C_{18}H_{15}NO_3$ (293,31)	235...237 ($CHCl_3$)	3422 (NH), 3222 (NH), 1674 ($CONH_2$), 1664 (C=O)	1,71, 1,95, 2,45 (3H, d.d), 5,68...5,84 (2H, m, NH_2), 5,95 (s, 2-H), 6,9...7,8 (9H, m, arH)	293 (5), 292 (15), 249 (75), 247 (100), 222 (15), 129 (40), 120 (55), 104 (15)	43
IVf	$C_{18}H_{15}NO_3$ (293,31)	206...207 ($CHCl_3$)	3430 (NH), 3250 (NH), 1654 ($CONH_2$), 1660 (C=O)	1,45, 2,30, 2,30 (3H, d.d), 5,68...5,65 (2H, m, NH_2), 5,23 (s, 2-H), 6,9...7,8 (9H, m, arH)	293 (10), 292 (20), 249 (70), 247 (100), 222 (10), 129 (35), 120 (50), 104 (10)	63

TABLE 1. (Continued)

Compound	Empirical formula	Mp, °C (solvent)	IR spectrum (KBr), ν, cm^{-1}	PMR spectrum, δ, ppm ($CDCl_3$)	Mass spectrum, m/z, %	Yield, %
1	2	3	4	5	6	7
IIg	$C_{19}H_{16}O_4$ (308,32)	101...104 (MeOH)	1716 (COOMe), 1684 (C=O)	1,63, 2,14, 2,53 (3H, d.d.), 3,75 (3H, s, COOMe), 5,95 (s, 2-H), 6,9...7,8 (9H, m, arH)	308 (12), 307 (28), 293 (23), 275 (10), 249 (95), 244 (100), 221 (25), 121 (90), 104 (95	95
IIIg	$C_{19}H_{16}O_4$ (308,32)	115...117 (MeOH)	1734 (COOMe), 1682 (C=O)	0,98, 2,09, 2,18 (3H, d.d.), 3,60 (3H, s, COOMe), 5,65 (c, 2-H), 7,0...8,0 (9H, m, arH)	308 (20), 293 (5), 277 (10), 249 (80), 221 (20), 121 (60), 221 (25), 121 (90), 104 (100)	81
IVg	$C_{19}H_{16}O_4$ (308,32)	96...98 (hexane)	1740 (COOMe), 1684 (C=O)	1,57*, 2,22, 2,63 (3H, d.d.), 3,25 (3H, s, COOMe), 5,55 (c, 2-H), 7,0...7,6 (9H, m, arH)	308 (16), 307 (13), 293 (9), 277 (8), 249 (94), 247 (60), 221 (25), 121 (63), 104 (100)	90
V	$C_{18}H_{13}NO_2$ (275,29)	168...170 (EtOH)	2370 (CN), 1646 (C=O)	1,3 (3H, d, Me), 3,75 (1H, q. CH), 7,5...8,4 (9H, m, arH)	275 (45), 274 (100), 259 (20), 248 (5), 246 (8), 129 (10)	65
VI	$C_{18}H_{14}N_2O_2$ (290,31)	215...217 (EtOH)	3428, 3214 (NH), 1664 (CONH)	1,15, 2,05, 2,45 (3H, d.d.), 5,10 (s, 2-H), 7,0...7,7 (9H, m, arH), 11,10 (1H, NH)	275 (45), 274 (100), 259 (20), 248 (5), 246 (8), 129 (10)	75
VII	$C_{18}H_{14}N_2O_2$ (290,31)	301...303 (EtOH)	3326, 3202 (NH), 1663 (CONH)	0,78, 1,20, 1,40 (3H, d.d.), 5,67 (s, 2-H), 7,1...7,9 (9H, m, arH), 11,10 (1H, NH)	290 (100), 261 (35), 247 (100), 186 (20), 131 (40)	88

*Spectrum in DMSO-D_6.

TABLE 2. Vicinal $^{13}C-^{1}H$ J Values for IId-IVd

Compound	$^{2}J_{2\text{-H,C(4)}}$	$^{2}J_{2\text{-H,C(8a)}}$	$^{2}J_{2\text{-H,CN}}$	Orientation of 2-H
IId	5,5	7,5	3,6	*e*
IIId	1,8	1,0	6,7	*a*
IVd	3,7	5,0	2,6	?

TABLE 3. Values of the Increase in Signal Intensities in the NOE Experiments, T

Compound	Irradiated proton	Proton for which the NOE is observed			
		A-H*	B-H*	X-H*	2-H
IId	A-H	×	30,5	12,9	—
	B-H	24,8	×	—	7,2
	X-H	5,6	—	×	2—4
	2-H	—	3,0	0,7	×
IIId	A-H	×	36,5	10,2	2,7
	B-H	29	×	—	—
	X-H	2,8	—	×	—
	2-H	—	—	—	×
IVd	A-H	×	37,5	13,2	2,2
	B-H	28,1	×	—	—
	X-H	7,4	3,0	×	—
	2-H	—	—	7,1	×

*The symbols A and B denote the geminal protons of the cyclopropane ring and X the proton at the CN substituent.

bischloromethyl derivative Ic using thionyl chloride. Treatment of Ib and Ic with potassium cyanide gives the nitriles IId, IIId, and IVd as a three diastereomer mixture. They can be separated by column chromatography. Hydrolysis of these nitriles using sodium hydroxide can occur differently. Nitriles IIId and IVd are hydrolyzed readily to give acids IIIe and IVe. Under the same conditions the hydrolysis of nitrile IId occurs slowly to give a mixture of acid IIe and amide IIf. The hydrolysis of nitriles IIId and IVd in a mixture of HCOOH and HCl gives flavone V. Under these conditions, nitrile IId yields a mixture of starting material and unidentified products. Treatment of acids IIe, IIIe, and IVe with diazomethane gives the methyl esters IIg, IIIg and IVg respectively.

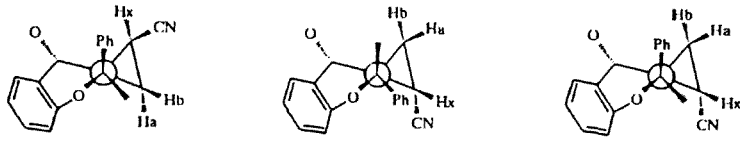
The stereochemistry of II-IV was determined from spin–spin coupling values (J) described for the cyclopropane ring [5, 7] and from experiments to measure homonuclear nuclear Overhauser effects (NOE). The analytical and spectroscopic parameters for the compounds investigated are given in Table 1. The J values for the cyclopropane fragment of the prepared nitriles are: $^{3}J_{trans}$ = 6.4-6.6, $^{3}J_{cis}$ = 9.3, $^{2}J_{gem}$ = 4.6-5.4 Hz.

Cyclization of acids IIIe, IVe with hydrazine hydrate in refluxing ethanol gives the pyridazin-3(2H)-ones VI, VII. Under the same conditions IIe gives a mixture of unidentified products. The structure of isomers VI and VII was confirmed by NMR (Table 1).

Using ethyl bromoacetate in the presence of sodium hydride in tetrahydrofuran, the pyridazinone VII was converted to VIIIa from which LiOH hydrolysis in methanol gave acid VIIIb.

The stereochemistry of the tricyclics II-IV was established using NMR spectroscopy. Because the proton J values for the three spin system of the cyclopropane ring gave little information, the NOE values of the individual protons were used for this purpose. Examination of molecular models showed that the γ-pyrone ring can have two equally probable conformations in which the 2-H proton has a quasiaxial or quasiequatorial orientation. Since the distance from proton 2-H to the cyclopropane ring protons is closely related to the orientation of 2-H, this had to be determined first. It was solved by measurement of the vicinal J $^{13}C-^{1}H$ values from two dimensional J spectroscopy. These J values for IId-IVd are given in Table 2.

In IId the largest J, observed for C_4 and C_{8a}, are explained by an antiperiplanar arrangement of the interacting partner relative to the C_1-C_2 and C_2-C_3 bonds respectively. Hence proton 2-H has an equatorial orientation in IId. In IIId the J described above is significantly less pointing to an axial orientation of 2-H.For IVd the J value has an intermediate value, hence the exact orientation of 2-H is not possible by this method. With this information in hand the position of the hydrogens in the



IId IIId IVd

Fig. 1. Newman projection of nitriles IId-IVd along the pyranone C_2-C_3 bond.

cyclopropane ring relative to 2-H can be deduced using NOE experiments. It will be assumed that x-H represents the proton of the cyclopropane fragment found at the atom bound by the nitrile group, *a*-H the proton cis to x-H, and b-H the proton trans to x-H.

In compound IId the intensity of the signal for b-H is slightly increased upon irradiation at the 2-H proton frequency but for x-H remains unchanged. Irradiation at b-H leads to a marked NOE (about 8%) for proton 2-H and no effect on x-H whereas irradiation at *a*-H gives a strong NOE increase (12.9%) for x-H (Table 3). These experiments point to the steric proximity of protons 2-H and b-H on the one hand and *a*-H and x-H on the other. Moreoever, 2-H and x-H are sterically remote in the molecule. These observations agree with a single structure in which the nitrile group is bound to the cyclopropane carbon atom close to the axial 2-phenyl group. From another viewpoint, the nitrile group is placed opposite the chromanone carbonyl.

As abbreviated stereochemical nomenclature for IId we will use the symbols ECT, where E corresponds to an equatorial orientation of proton 2-H, C to a cisoid orientation of the nitrile group and the phenyl substituent, and T to a transoid orientation of the nitrile group and the chromanone carbonyl. Figure 1 shows a Newman projection of molecule IId along the C_2-C_3 bond in the pyranone ring.

In IIId the 2-H proton is orientated axially and the phenyl substituent equatorially. In contrast to the discussion above for IId, irradiation at the *a*-H frequency leads to a weak NOE for the 2-H signal. By contrast, irradiation of *a*-H gives a marked increase in intensity for x-H. Examination of a steric model shows that the distance between protons *a*-H and 2-H increases significantly when the orientation changes from axial to equatorial (from 2.3 to 2.9 Å). The fact that the signal for *a*-H is very powerfully relaxed by its geminal partner b-H can readily account for the small NOE between *a*-H and 2-H. In line with the indications adopted for IId the stereochemistry of IIId can be designated ACC (2-H axial, CN and phenyl cisoid, C=O and CN also directed to one side). The Newman projection of IIId is given in Figure 1.

In IVd a marked NOE is observed between 2-H and x-H. Hence the CN group is aligned on the same side as the chromanone carbonyl. The NOE value (7.1%) supports an equatorial orientation for 2-H. The large value when compared with IId is evidently connected with the absence of the efficiently relaxing geminal partner in this case. The stereochemistry can be defined as ETC (see Figure 1).

Further confirmation of the above assignment of structures can be obtained by analyzing the changes in the spectra of IId-IVd induced by lanthanide shift reagents (LSR).

A study of the behavior of the nitriles with LSR has shown that one of them (IId) interacts with $Eu(FOD)_3$ much more efficiently than the other two. Thus the individual lanthanide induced shifts (LIS) are much greater for IId than for IIId or IVd. In IId the LIS for the 2-H and 5-H protons of the chromanone ring are found to be 4.3 and 8.8 ppm whereas in IVd they are 2.8 and 3.3 and in IIId 1.9 and 2.8 ppm respectively. The highest LIS were found for protons nearest to the chromanone carbonyl oxygen atom. Hence this is the most effective coordination site in the studied molecules. It is also known that the ability of a molecule to react with an LSR is extremely sensitive to steric hindrance around the coordination site. In isomers IId-IVd the single factor which can influence coordination with an LSR is the orientation of the CN group in the cyclopropane ring. If this group and the chromanone carbonyl have a cisoid orientation the interaction of the molecule with the LSR can be hindered. Such a situation is observed in IIId and IVd. On the other hand, in IId the nitrile group has a transoid orientation with respect to the carbonyl and does not inhibit its coordination with the LSR. Hence the ease of interaction of IId-IVd with the LSR can clarify the orientation of the nitrile group relative to the chromanone carbonyl.

Structural evidence for IVd also comes from analysis of the chemical shift values for the protons in the cyclopropane ring. If one compares the spectral parameters for IVd with those for IId it appears that the signals for the A-H and B-H methylene protons, particularly in deuterobenzene, have inverse chemical shift values. In IId the proton signal having a trans constant of 6.5 Hz is found at 0.54 ppm and the proton with a cis constant of 9.3 Hz is at 1.92 ppm. By contrast, in IVd the

proton with a trans constant is at 1.86 ppm and that with a cis constant at 0.51 ppm. Thus IVd differs from IId only in the orientation of the nitrile group. This is in full agreement with the structural assignments made above for these compounds.

NOE experiments with esters IIg-IVg show that the compound configurations do not change upon hydrolysis of nitriles IId-IVd to amides IIf-IVf or acids IIe-IVe. Epimerization does not occur during hydrazinolysis since IIIe and IVe form the tetracyclic pyridazines VI and VII whereas IIe does react.

EXPERIMENTAL

Melting points were determined using a Kofler heating apparatus. NMR spectra were measured on Bruker WP-200 SY and WP-100 SY instruments with TMS internal standard. IR Spectra were taken on a Perkin-Elmer 283 machine. Mass spectra were recorded on a VG-7035 instrument by electron impact using an accelerating voltage of 70 eV. Kieselgel 40 or 60 (Merck, 0.063-0.2 mm) was used for chromatography.

Elemental analytical data for the compounds prepared agreed with those calculated.

3,3-Bis(hydroxymethyl)flavanone (Ia) was obtained by a reported method [6] starting from flavanone and formaldehyde in dioxan in the presence of Na_2CO_3.

3,3-Bis(chloromethyl)flavanone (Ic). A mixture of Ia (2.8 g, 10 mmole), thionyl chloride (10 ml), and DMF (1 ml) was heated at 100°C for 48 h. After cooling, the volatile components were evaporated *in vacuo* and the residue chromatographed on silica gel using hexane–ethyl acetate (4:1). Ic (1.4 g, 45%) was obtained as white crystals with mp 120-122°C (from a mixture of hexane and ethyl acetate). IR spectrum (KBr): 1698 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.0-7.1 (9H, m, ArH), 5.9 (1H, s, 2-H), 4.5, 3.3 (2H, d, J = 10 Hz, CH_2), 4.0, 3.5 (2H, d, J = 10 Hz, CH_2).

2-Cyano-(flavanone-3-spiro-1″-cyclopropanes) IId, IIId, IVd. A. A solution of KCN (0.55 g, 8.5 mmole) in DMSO (50 ml) was added dropwise with stirring to a solution of Ic (1.3 g, 4 mmole) in DMSO (20 ml) at 100°C. After 20 h at ~20°C the product was poured into water (100 ml) and extracted with ether. After evaporation of solvent the mixture was separated on a column using hexane–ethyl acetate (4:1) to give IId first eluting followed by IIId and finally IVd.

B. KCN (22 g, 0.33 mole) was added to a solution of Ib (20 g, 33.7 mmole) in DMSO (100 ml) and stirred at 100°C for 6 h. The product was poured onto ice (1 liter) and the precipitate (8.9 g, 96%) filtered and separated as above to give the cyano derivatives IId, then IIId and finally IVd (Table 1).

2″-Carboxy(flavanone-3-spiro-1″-cyclopropanes) IIe, IIIe, IVe and 2″-Carboxamido(flavanone-3-spiro-1″-cyclopropanes) IIf, IVf. A solution of nitrile IId (0.55 g, 2 mmole) in ethanol (30 ml) was heated (~100°C) with an 8% solution of sodium hydroxide (6 mmole) for 20 h. Pouring the product into water and filtration gave a precipitate of the carboxamide IIf. Removal of ethanol solvent from the solution *in vacuo*, addition of a mixture of hydrochloric acid and water (1:1), and filtration gave the carboxy compound IIe (see Table 1).

Compounds IIIc and IVc were obtained similarly from nitriles IIId and IVd (see Table 1). IVf was prepared from IVd using K_2CO_3 and 30% H_2O_2 at 0°C.

Methyl(flavanone-3-spiro-1-cyclopropane-2-carboxylates) IIg, IIIg, IVg. A solution of diazomethane in ether (10 ml) was added to solutions of IIe, IIIe, or IVe (1 mmole) in methylene chloride (25 ml) and kept for 20 h in a fridge. Evaporation of solvent and treatment of the residue with aqueous $NaHCO_3$ gave methyl carboxylates IIg, IIIg, or IVg (Table 1).

3-(1-Cyanoethyl)flavone (V). Nitrile IIId or IVd (1 mmole) was refluxed with formic acid (10 ml) and HCl (36%, 5 ml) for 10 h. Evaporation, addition of a solution of $NaHCO_3$ to the residue, and filtration gave flavone V in 60-65% yield (Table 1). On the basis of TLC evidence a similar reaction of nitrile IIe does not occur.

3a,4a-Dihydro(5-phenyl)benzopyrano[4,3-c]cyclopropane[d]-pyridazin-3-(2H)-ones VI, VII. Hydrazine (70%, 10 ml) was added to a solution of IIIe or IVe (10 mmole) in ethanol (50 ml) and heated at 100°C for 6 h. The mixture was cooled in the fridge and filtered to give VI or VII (see Table 1). Under these conditions IIe gave a mixture of unidentified products.

3a,4a-Dihydro(5-phenyl)benzopyrano[4,3-c]cyclopropane[d]-(2-N-carbethoxymethylene)pyridazin-3-(2H)-one (VIIIa). Sodium hydride (0.6 g, 30 mmole) in oil (88%) was added to a solution of pyridazinone VII (3 g, 10.3 mmole) in absolute THF (100 ml) at 20°C. After 1 h ethyl bromoacetate (2 g, 15 mmole) was added dropwise with stirring. The mixture was stirred at about 20°C for 20 h, poured into water (100 ml), and extracted with ethyl acetate. After evaporation of solvent the residue was crystallized from hexane–ethyl acetate to give VIIIa (2.8 g, 73%) as white crystals with mp 126-128°. PMR spectrum ($CDCl_3$): 0.9, 1.10, 1.85 (3H, dd), 1.3 (3H, t, CH_3), 4.6 (2H, m, N-CH_2), 5.5 (1H, s, 5-H), 7.0-8.0 ppm (9H, m, ArH).

3a,4a-Dihydro(5-phenyl)benzopyrano[4,3-c]cyclopropane[d]-(2-N-carboxymethylene)pyridazin-3-one (VIIIb). LiOH (1 g) in water (25 ml) was added to a solution of ester VIIIa (2.5 g, 6.6 mmole) in methanol (130 ml) and stirred at ~20°C for 16 h. Addition of water and HCl and separation gave VIIIb as a white precipitate (2.2 g, 95%). PMR Spectrum (DMSO-D_6): 0.85, 1.25, 1.6 (3H, dd), 4.5 (2H, m, $N-CH_2$), 5.75 (1H, s, 5-H), 7.0-8.0 ppm (9H, m, Ar).

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