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Pyridazinium Ylides. Regiochemistry of Addition

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For the first time in the pyridazine series we have accomplished a theoretical and experimental study of the regiochemistry of the 3+2 dipolar cycloadditions of 3-(4-halophenyl)pyridazinium ylides to acrylonitrile. The reactions are regioselective, the ratio between the two isomers formed being 96:3. It is assumed that the major stereoisomers are formed by an *endo* approach of dipole (ylide)–dipolarophile (acrylonitrile) which is favoured energetically. The minor stereoisomers formed can be explained by an *exo* approach of the ylide–acrylonitrile which is disfavoured energetically. Eight new pyrrolopyridazine heterocycles have been obtained.

Previously we have described the cycloaddition of 3-(4-halophenyl)pyridazinium ylides to symmetrically substituted olefins[1] and alkynes[2,3] and to ethyl acrylate or propiolate as unsymmetrically substituted dipolarophiles.[4] The addition of pyridazinium ylides to unsymmetrically substituted olefins and alkynes is of interest because of the reaction mechanism and the possibility of preparing new pyrrolopyridazine heterocycles which otherwise are difficult to obtain. Therefore we have conducted a theoretical and experimental study regarding the regiochemistry of the reactions of 3-(4-halophenyl)pyridazinium ylides with acrylonitrile (Fig. 1).

The problem of orientation in cycloaddition reactions of cycloimmonium ylides to activated unsymmetrically substituted olefins and alkynes has interested many researchers[5–7] because the addition of the dipole to the dipolarophile in a double sense has often been found, in accordance with the steric and electronic factors (Fig. 4). Theoretical studies which have been done[8–10] regarding the regiochemistry of cycloaddition reactions of ylides (such as 1,3-dipoles) to unsymmetrically substituted activated olefins or alkynes (such as dipolarophiles), have made use of the general theory of perturbation limited to the frontier molecular orbitals.[10–14]

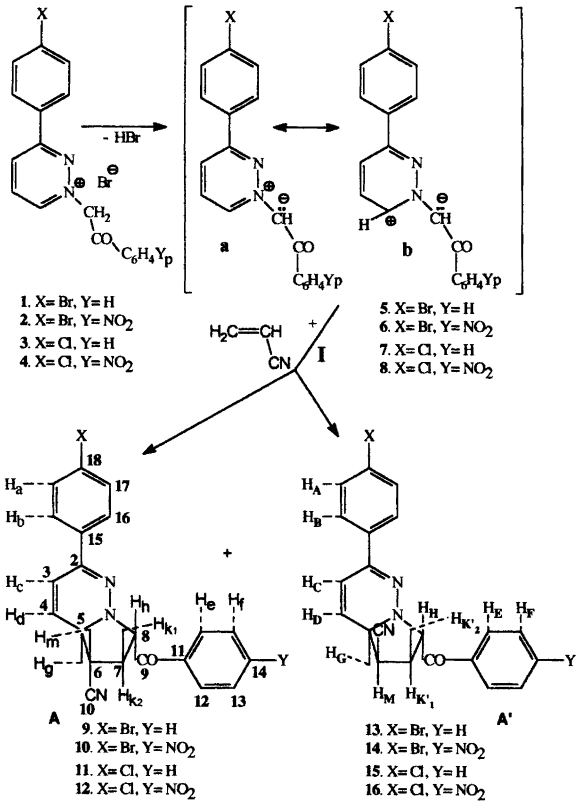

Fig. 1. Reaction between 3-(4-halophenyl)pyridazinium ylides and acrylonitrile.

Results and discussion

The first part of the paper is a theoretical study concerning the regiochemistry of cycloaddition reactions of 3-(4-halophenyl)pyridazinium ylides to acrylonitrile. We have used the general theory of perturbation limited to the frontier molecular orbitals. The atomic charges, the coefficients of the atomic orbitals and the values of the energy of the frontier molecular orbitals were calculated using the MNDO method (Table 1).[15,16]

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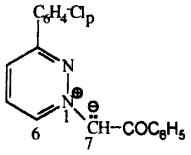
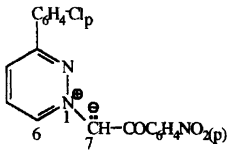
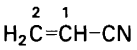
Table 1. The coefficients of atomic orbitals (p_z), the total atomic charge (in C) and energies (in eV) of ylides **7**, **8** and acrylonitrile.

Molecule	Orbital and atomic charge (Q)	*E*/eV	Coefficients of atomic orbitals, (p_z)		
			C6	**N1**	**C7(i)**
	HOMO	−7.8802	*0.3344*	−0.1031	*−0.7341*
	LUMO	−1.1810	0.4995	−0.2758	0.2628
	Q		**−0.0517**	0.2643	**−0.3120**
			C6	**N1**	**C7(i)**
	HOMO	−8.2528	0.3314	−0.0921	*−0·7399*
	LUMO	−1.8160	0.1267	−0.1114	0.0444
	Q		**−0.0598**	0.2621	**−0.3223**
			C1	**C2**	
	HOMO	−10.6763	−0.6510	−0.6503	
	LUMO	0.0927	*0.5793*	*−0.6975*	
	Q		**−0.0319**	**−0.0112**	

The geometry of pyridazinium ylides **5**–**8**, and acrylonitrile was approximated using data from the literature.[5,6] Analysis of these data led to the conclusion that 3-(4-halophenyl)pyridazinium ylides could have a 1,3-dipolar structure of type **5a**–**8a**, and, therefore, they can be used in cycloaddition reactions as 1,3-dipoles. In Table 1, we present the energies (in eV) of the frontier molecular orbitals (HOMO and LUMO), the coefficients of the atomic orbitals p_z, and the total atomic charges (in coulombs) of all the atoms involved in the cycloaddition reaction between ylides **7** and **8** and acrylonitrile. Making use of the data in Table 1, we have constructed correlation diagrams between the HOMO and LUMO orbitals of the ylides and dipolarophiles (Fig. 2).

Analysis of the correlation diagrams shows that the interactions HOMO ylide–LUMO dipolarophile are characterised by the lowest interaction energies ($\Delta E_1 =$ 7.9729 eV for ylide **7** and $\Delta E_2 = 8.3455$ eV for ylide **8**).

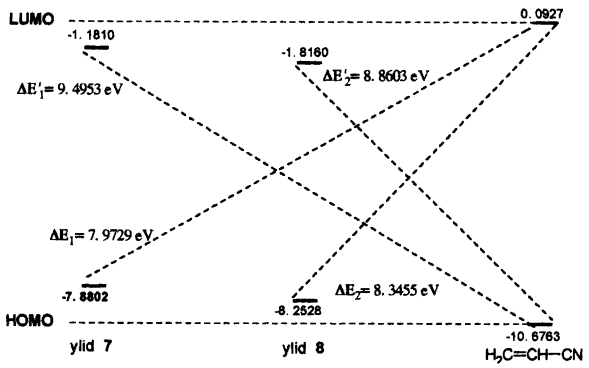


Fig. 2. Correlation diagram between ylides **7** and **8** and acrylonitrile.

This means that, in a reaction ylide (donor)–dipolarophile (acceptor), under orbital or charge control, the most likely interaction will take place between the C3 atom from the ylide and C2 from acrylonitrile (Fig. 3).

As Fig. 4 shows, in the case of reactions between cycloimmonium ylides with acrylonitrile, theoretically, there could be two reaction pathways (**I** and **II**) with the formation of two pairs of regioisomers (**A**, **A′** and **B**, **B′**). But analysing the data presented before, we find that, in the case of pyridazinium ylides, the bond is formed between the ylide carbon and the unsubstituted carbon atom from the acrylonitrile. This is in accordance with the electronic effects exerted by the acrylonitrile, which means that the reaction is under a charge control (path **I**, stereoisomer **A** and **A′**, Fig. 4).

Pathway **I** of the reaction was also predicted (and confirmed) by the formation energies of the final products. Thus, as can be seen in Table 2, the formation energies increase in the order **A** > **A′** > **B′** > **B**. That means that the stereoisomers **A** (**9**–**12**) and **A′** (**13**–**16**) are more stable, and have the highest probability of formation.

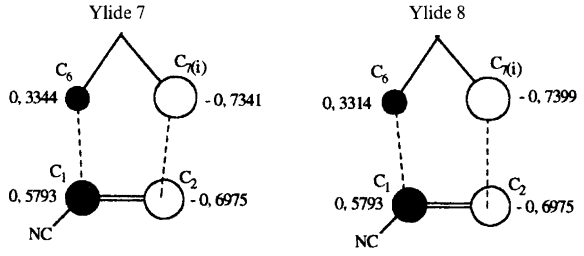


Fig. 3. Graphical representation of the interaction between the frontier molecular orbitals.

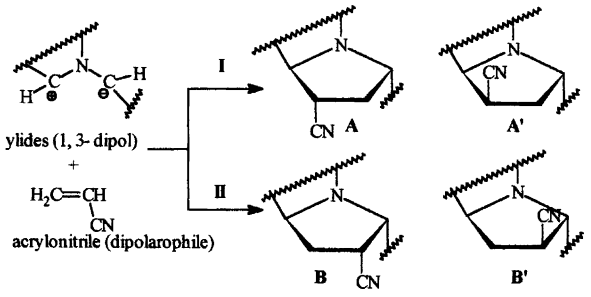


Fig. 4. Reaction pathway between ylides and acrylonitrile.

Table 2. Formation energies for the final products.

Final products X=Cl; Y=H	*E*/kcal mol^{-1}	Final products X=Cl; Y=NO_2	*E*/kcal mol^{-1}
11 A	**193.102**	**12 A**	**233,021**
15 A'	*195.286*	**16 A'**	*235.179*
B'	196.802	**B'**	236.687
B	198.010	**B**	237.036

In order to verify the theoretical data presented, we carried out the 3+2 cycloaddition reactions between 3-(4-halophenyl)pyridazinium ylides **5–8** (which were obtained *in situ* from the corresponding cycloimmonium salts)[17] and acrylonitrile (Fig. 1). As can be seen in Fig. 1, a single regioisomer is obtained (according to the pathway **I** from Fig. 4) and both stereoisomers **A** (major, 96%) and **A'** (minor, 3%). We consider that the major **A** stereoisomers are formed by an *endo* approach of the dipole (ylide)–dipolarophile (acrylonitrile) which is energetically favoured. The formation of **A'** stereoisomers can be explained by an *exo* approach of the ylide–acrylonitrile which is disfavoured energetically (Fig. 5).

The structures of **A** (**9–12**)- and **A'** (**13–16**)-type products, were proved by elemental and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and MS). Obviously, the data furnished by the elemental analysis are compatible with both types of regioisomer. However, the data offered by the spectral analysis confirm that **A**- and **A'**-type products are obtained, according to the **I** route, which means that the reaction is under a charge control. Thus, analysis of the spectra, such as that of product **9** (representative of series **A**) and **13** (representative of series **A'**), reveals the following data.

In the IR spectra the most important signals are those of the cyano group at 2245 cm^{-1} (low intensity) and the ketone group at 1675 cm^{-1} (very intense).

The ^{1}H NMR spectra supply essential data concerning the structure of the products. The most important protons in assigning the structure of product **9** are H_c, H_d, H_g, H_m, H_{k1}, H_{k2} and H_h. Thus, the H_h proton appears between 5.69–5.63 ppm, as two doublets, which excludes the **B** and **B'** structures (where these protons should appear under the form of a doublet). The H_h proton has two different coupling constants, $J_{hk2}=8.5$ Hz and $J_{hk1}=3.5$ Hz, which show that it is *trans* to H_{k2} and on the same side of the pyrrolo ring as H_{k1}. H_{k1} and H_{k2} appear as non-equivalent protons: H_{k1} at 2.27–2.14 ppm (eight lines $2\times2\times2$, $J_{k1m}=4.4$ Hz, $J_{k1h}=3.5$ Hz, $J_{k1k2}=13.3$ Hz) and H_{k2} at 2.75–2.62 ppm (eight lines $2\times2\times2$, $J_{k2m}=9.2$ Hz, $J_{k2h}=8.51$ Hz, $J_{k2k1}=13.3$ Hz). The coupling constants confirm their position in the pyrrolo ring (H_{k1} is up and H_{k2} is down) and show us that H_m proton is above the ring (this is also confirmed by the chemical shift 3.31–3.21 ppm of this proton and its coupling constants, eight lines $2\times2\times2$, $J_{mk1}=4.4$ Hz, $J_{mk2}=9.2$ Hz, $J_{mg}=6.5$ Hz). At 4.14–4.07 ppm there is a signal due to H_g (two doublets and a triplet, $J_{gm}=6.5$ Hz, $J_{gd}=4.9$ Hz and a long range coupling $J_{gc}=1.3$ Hz) which show that H_g is above the ring. Making use of these data we conclude that isomer **9** has a tetrahydropyrrolopyridazine structure in which the cyano group is below the ring and the protons are above and below the ring as shown in Fig. 6.

An ^{1}H NMR spectral analysis of **13** was carried out in the same manner and indicated that this isomer has a **A'**-type structure in which the cyano group is above the ring (Fig. 6).

In the ^{13}C NMR spectra the most important signals

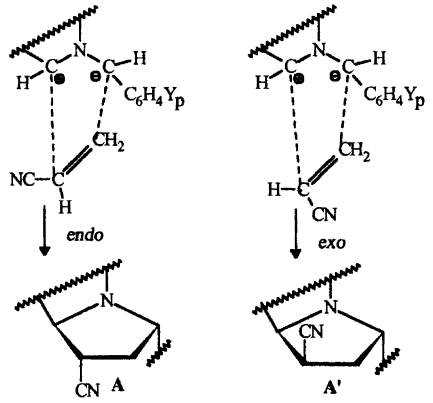


Fig. 5. Mechanism of approach of dipole–dipolarophile.

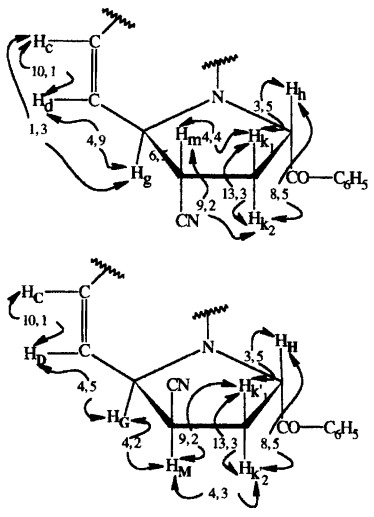


Fig. 6. Regioisomer structures.

are the signals of ketone carbon (C9, 194.24 ppm) and the carbons from the pyrrolo ring [C8, 69.77 ppm (α pyrrolo ring, α ketone carbon); C5, 35.81 ppm (α pyrrolo ring); C6, 35.18 ppm (β pyrrolo ring, α cyano carbon), C7, 28.77 ppm (β pyrrolo ring, α aliphatic carbon).

MS also confirmed the proposed structures. Thus, the molecular ion, the $M+1$, $M+2$, $M-1$ and $M-2$ peaks, the main fragmentation reaction (α on the ketone group) and the remaining fragments confirm the structures.

Conclusions

1. The cycloaddition reactions between 3-(4-halophenyl)-pyridazinium ylides and acrylonitrile are regioselective. The reaction is HOMO controlled from the ylide, and only one regioisomer is formed (and both stereoisomers), namely the one in which the ylide carbanion makes a new bond with the most electrophilic carbon from acrylonitrile. The theoretical and experimental data are in accordance with each other.

2. As a mechanism, we consider that the major stereoisomers are formed by an *endo* approach of the dipole (ylide)–dipolarophile (acrylonitrile) which is favoured energetically. The minor stereoisomers formed could be explained by an *exo* approach of the ylide–acrylonitrile which is disfavoured energetically.

3. Eight new pyrrolopyridazine heterocycles have been made.

Experimental

^{1}H NMR spectra were run on a Gemini 200 MHz or Bruker 80 MHz spectrometer and were recorded in ppm downfield from an internal standard, $SiMe_4$ in $CDCl_3$. The coupling constants are given in Hz. The ^{13}C NMR spectra were recorded on a Gemini 200 MHz spectrometer. The mass spectra were recorded at 10 kV ionising voltage, using field desorption (FD). The IR spectra were recorded with a SPECORD-71 spectrometer in KBr.

General procedure. The cycloimmonium salt (1 mmol) was suspended in 20 ml anhydrous benzene. Acrylonitrile (1 mmol) and triethylamine (1 mmol) dissolved in 3 ml benzene were then added. The solution was heated to reflux for 2 h and the solvent evaporated off on a steam bath. The crude product was recrystallized from an appropriate solvent, to give the **A**-type products. The residual material from recrystallization was evaporated and the two isomers, **A** and **A'**, were purified by flash chromatography on silica gel using hexane–EtOAc 8:2 (v/v).

*2-(4-Bromophenyl)-5-cyano-7-benzoyl-4a,5,6,7-tetrahydro-4a*H*-pyrrolo[1,2-*b*]pyridazine* **A** (**9**). Recrystallized from ethanol. Yellow acicular crystals. Yield 96%, m.p. 153–154 °C. Anal. ($C_{21}H_{16}BrN_3O$: C, H, N; IR (KBr, cm^{-1}): 2245 (w), 1675 (s), 1605, 1495, 1450, 1410 (s–m), 3100–3000 (w). ^{1}H NMR ($CDCl_3$): δ 8.17–8.12 (dd, 2 H_b, J_{ba} = 8.3 Hz), 7.64–7.45 (m, 2 H_e, 1 H_y, 2 H_a, 2 H_f), 6.61–6.55 (dd, 1 H_c, J_{cd} = 10.1 Hz, J_{cg} = 1.3 Hz), 6.21–6.13 (dd, 1 H_d, J_{dc} = 10.1 Hz, J_{dg} = 4.9 Hz), 5.69–5.63 (dd, 1 H_h, J_{hk2} = 8.5 Hz, J_{hk1} = 3.5 Hz), 4.15–4.07 (m, ddd, 1 H_g, J_{gd} = 4.9 Hz, J_{gm} = 6.5 Hz, J_{gc} = 1.3 Hz), 3.31–3.21 (ddd, 1 H_m, J_{mk2} = 9.2 Hz, J_{mg} = 6.5 Hz, J_{mk1} = 4.4 Hz), 2.75–2.62 (ddd, 1 H_{k2}, J_{k2k1} = 13.3 Hz, J_{k2h} = 8.5 Hz, J_{k2m} = 9.2 Hz), 2.28–2.14 (ddd, 1 H_{k1}, J_{k1k2} = 13.3 Hz, J_{k1h} = 3.5 Hz, J_{k1m} = 4.4 Hz). ^{13}C NMR ($CDCl_3$): δ 194.24 (C9), 141.12 (C14), 134.21 (C15), 133.99 (C11), 133.11 (C17), 130.83 (C12), 128.62 (C13), 128.02 (C16), 125.92 (C18), 124.26 (C2), 121.91 (C3), 119.44 (C10), 118.78 (C4), 69.77 (C8), 55.81 (C5), 35.17 (C6), 28.77 (C7). MS (EI): 405 (M^+, 10%), 406 (3.5), 407 (8.5), 404 (4), 403 (14), 352 (27), 326 (6), 300 (63), 273 (21), 249 (13), 234 (75), 182 (56), 105 (PB, 100%), 91 (8), 77 (73).

*2-(4-Chlorophenyl)-5-cyano-7-benzoyl-4a,5,6,7-tetrahydro-4a*H*-pyrrolo[1,2-*b*]pyridazine* **A** (**11**). Recrystallized from acetonitrile. Yellow acicular crystals. Yield 95%, m.p. 147–148 °C. Anal. ($C_{21}H_{16}ClN_3O$: C, H, N; IR (KBr, cm^{-1}): 2240 (w), 1685 (s), 1600, 1495, 1455, 1410 (s–m), 3100–3000 (w). ^{1}H NMR ($CDCl_3$): δ 8.35 (d, 2 H_b, J_{ba} = 8.5 Hz), 7.95–7.33 (m, 2 H_e, 1 H_y, 2 H_a, 2 H_f), 6.68 (d, 1 H_c, J_{cd} = 10.0 Hz), 6.3 (dd, 1 H_d, J_{dc} = 10.0 Hz, J_{dg} = 4.0 Hz), 5.84 (dd, 1 H_h, J_{hk2} = 8.0 Hz, J_{hk1} = 3.3 Hz), 4.35 (t, 1 H_g, J_{gd} = 4.0 Hz, J_{gm} = 6.5 Hz), 3.42 (m, 1 H_m, J_{mk2} = 9.0 Hz, J_{mg} = 6.5 Hz, J_{mk1} = 4.0 Hz), 2.85 (m, 1 H_{k2}, J_{k2k1} = 12.5 Hz, J_{k2h} = 8.0 Hz, J_{k2m} = 9.0 Hz), 2.28 (m, 1 H_{k1}, J_{k1k2} = 12.5 Hz, J_{k1h} = 3.3 Hz, J_{k1m} = 4.0 Hz).

*2-(4-Bromophenyl)-5-cyano-7-(4-nitrobenzoyl)-4a,5,6,7-tetrahydro-4a*H*-pyrrolo[1,2-*b*]pyridazine* **A** (**10**). Recrystallized from ethanol. Yellow acicular crystals. Yield 94%, m.p. 204–206 °C. Anal. ($C_{21}H_{15}BrN_4O_3$: C, H, N. IR (KBr, cm^{-1}): 2245 (w), 1670 (s), 1530, 1355 (s), 1600, 1500, 1455, 1415 (s–m), 3100–3000 (w). ^{1}H NMR ($CDCl_3$): δ 8.65–8.32 (m, 2 H_f, 2 H_e), 7.68–7.33 (m, 2 H_b, 2 H_a), 6.75 (d, 1 H_c, J_{cd} = 10.0 Hz), 6.3 (dd, 1 H_d, J_{dc} = 10.0 Hz, J_{dg} = 4.0 Hz), 5.75 (dd, 1 H_h, J_{hk2} = 8.0 Hz, J_{hk1} = 3.5 Hz), 4.10 (t, 1 H_g, J_{gd} = 4.0 Hz, J_{gm} = 6.5 Hz), 3.40 (m, 1 H_m, J_{mk2} = 9.0 Hz, J_{mg} = 6.5 Hz, J_{mk1} = 4.0 Hz), 2.90 (m, 1 H_{k2}, J_{k2k1} = 13.0 Hz, J_{k2h} = 8.0 Hz, J_{k2m} = 9.0 Hz), 2.33 (m, 1 H_{k1}, J_{k1k2} = 12.0 Hz, J_{k1h} = 3.5 Hz, J_{k1m} = 4.0 Hz).

*2-(4-Chlorophenyl)-5-cyano-7-(4-nitrobenzoyl)-4a,5,6,7-tetrahydro-4a*H*-pyrrolo[1,2-*b*]pyridazine* **A** (**12**). Recrystallized from acetonitrile. Yellow acicular crystals. Yield 95%, m.p. 170–171 °C. Anal. ($C_{21}H_{15}ClN_4O_3$: C, H, N. IR (KBr, cm^{-1}): 2245 (w), 1680 (s), 1530, 1355 (s), 1600, 1500, 1455, 1415 (s–m), 3100–3000 (w). ^{1}H NMR ($CDCl_3$): δ 8.65–8.30 (m, 2 H_f, 2 H_e), 7.80–7.35 (m, 2 H_b, 2 H_a), 6.7 (d, 1 H_c, J_{cd} = 10.0 Hz), 6.3 (dd, 1 H_d, J_{dc} = 10.0 Hz, J_{dg} = 4.0 Hz), 5.75 (dd, 1 H_h, J_{hk2} = 8.0 Hz, J_{hk1} = 3.5 Hz), 4.35 (t, 1 H_g, J_{gd} = 4.0 Hz, J_{gm} =

6.5 Hz), 3.45 (m, 1 H_m, J_{mk2}=9.0 Hz, J_{mg}=6.5 Hz, J_{mk1}=4.0 Hz), 2.90 (m, 1 H_{k2}, J_{k2k1}=13.0 Hz, J_{k2h}=8.0 Hz, J_{k2m}=9.0 Hz), 2.33 (m, 1 H_{k1}, J_{k1k2}=12.0 Hz, J_{k1h}=3.5 Hz, J_{k1m}=4.0 Hz).

2-(4-Bromophenyl)-5-cyano-7-benzoyl-4a,5,6,7-tetrahydro-4aH-pyrrolo[1,2-b]pyridazine **A'** (**13**). Yellow compound. Yield 3%, m.p. 150–152 °C. ^{1}H NMR ($CDCl_3$): δ 7.96–7.91 (d, 2 H_B, J_{BA}=10.0 Hz), 7.85–7.44 (m, 2 H_E, 1 H_Y, 2 H_A, 2 H_F), 6.50–6.45 (d, 1 H_C, J_{CD}=10.0 Hz), 6.42–6.35 (dd, 1 H_D, J_{DC}=10.0 Hz, J_{DG}=4.5 Hz), 5.62–5.55 (dd, 1 H_H, $J_{HK'2}$=8.5 Hz, $J_{HK'1}$=3.5 Hz), 4.02–3.94 (dd, 1 H_G, J_{GD}=4.5 Hz, J_{GM}=4.2 Hz), 3.20–3.05 (m, 1 H_M) 2.62–2.45 (h, 1 $H_{K'2}$, $J_{K'2K'1}$=13.3 Hz, $J_{K'2H}$=8.5 Hz, $J_{K'2M}$=4.3 Hz), 2.42–2.40 (h, 1 $H_{K'1}$, $J_{K'1K'2}$=13.3 Hz, $J_{K'1H}$=3.5 Hz, $J_{K'1M}$=9.2 Hz). Anal., IR, ^{13}C NMR and MS are identical with compound **9**.

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