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Pyridazines, LVIII [1]: 1-Phenyl-1-pyridazinyl-2-substituted Ethenes, Synthesis and Configuration**

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Summary. Starting from phenyl pyridazinyl ketones **1** and **3** various 1-phenyl-1-pyridazinyl-2-substituted ethenes (**2a–c, 4, 5a, b, 6a, b, 7–9**) were prepared by Wittig-Horner- oder Wittig-type reactions. Configurational assignments of these novel compounds were achieved by NOE difference spectroscopy.

Keywords. Phenyl-4-pyridazinylmethanone; Phenyl-3-pyridazinylmethanone; Phenyl-pyridazinyl-ethenes, configuration of; NOE-difference spectroscopy.

Pyridazine, 58. Mitt. [1]: Neue 2-substituierte 1-Phenyl-1-pyridazinylethene, Synthese und Konfiguration

Zusammenfassung. Aus den Phenyl-pyridazinylketonen **1** und **3** wurden mittels Wittig-Horner- bzw. Wittig-Reaktion die 2-substituierten Phenyl-pyridazinylethene **2a–c, 4, 5a, b, 6a, b, 7–9** dargestellt. Die Aufklärung der Konfiguration dieser neuen Verbindungen erfolgte mittels NOE-Differenzspektroskopie.

Introduction

The 1,1-diarylethene system represents an essential subunit of a wide variety of bio-active compounds. In particular, mono-aza congeners (i.e. 1-phenyl-1-pyridyl-2-substituted ethenes) have been investigated in detail and several interesting drugs (antidepressants [3, 5], nonsedating antihistaminics [5], antithrombotics [6–8]) emerged from these studies. Diaza-analogous systems in which one of the aryl moieties is a pyridazine nucleus, however, so far remained totally unexplored.

On the other hand, it has been shown recently that replacement of the azine system in certain pyridine-derived drug molecules [9–11] by the pyridazine system may afford compounds with improved biological activity or reduced cytotoxicity.

These findings now prompted us to investigate Wittig-Horner-type carbonyl-olefination reactions of phenyl pyridazinyl ketones in order to gain access to novel synthetic intermediates potentially useful for bio-isosterism studies. This approach

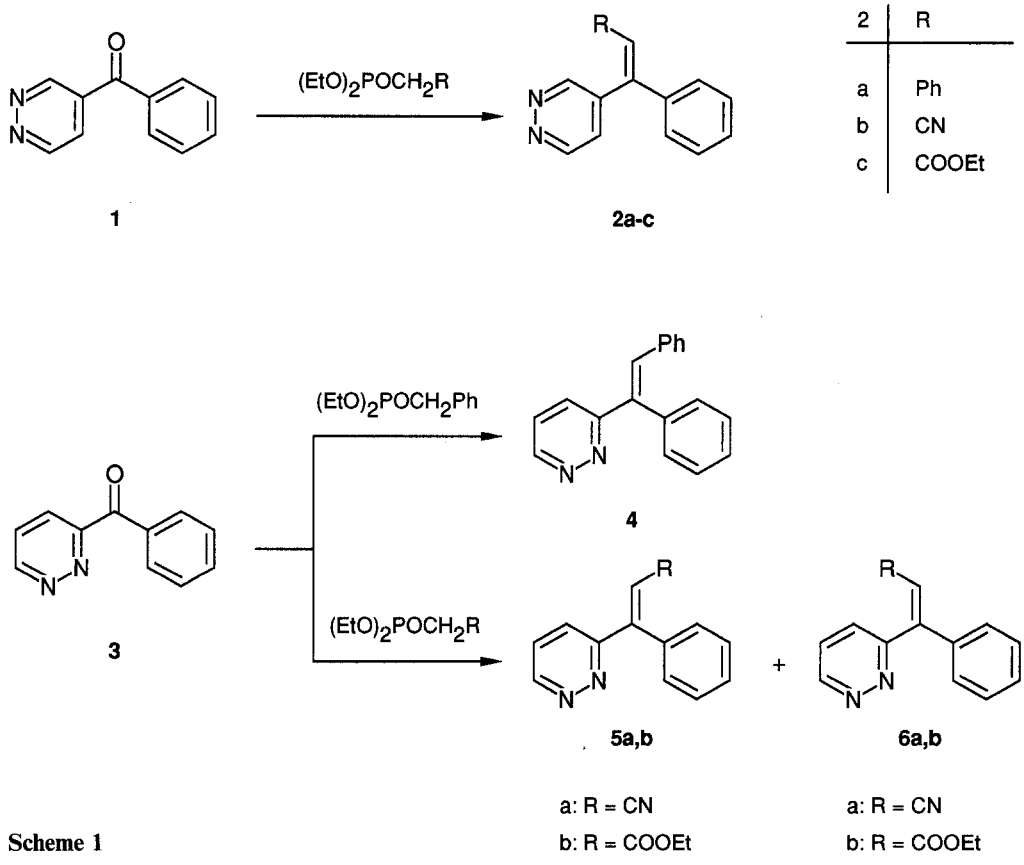
** Dedicated with best wishes to Prof. Dr. M. Pailer on the occasion of his 80th anniversary

to the title compounds was chosen in view of the convenient availability of phenyl 4-pyridazinyl ketone (**1**) [13, 14] and the isomeric 3-pyridazinyl derivative (**3**) [15, 16]. An economical large scale preparation for the latter ketone has been elaborated quite recently [2].

Results and Discussion

Syntheses

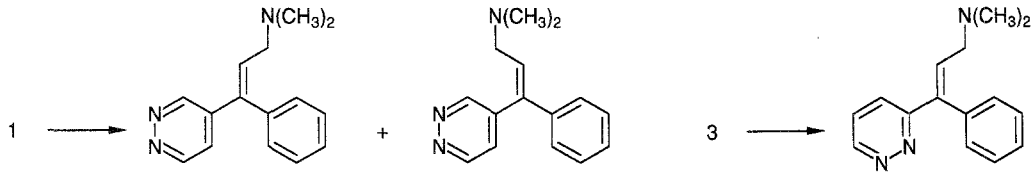
Phenyl 4-pyridazinyl ketone (**1**) was found to react smoothly with diethyl benzylphosphonate/sodium hydride (15 h, 25°) to afford a 70% yield of **2a**. Under these mild conditions we also succeeded in the preparation of the olefins **2b** and **2c** in satisfactory yields. Whereas these reactions of **1** afforded *Z*-isomers almost exclusively (only traces of the *E*-isomers could be detected by glc/ms), treatment of phenyl 3-pyridazinyl ketone (**3**) with diethyl cyanomethylphosphonate or diethyl ethoxycarbonylmethylphosphonate under analogous conditions gave mixtures of *Z* and *E* olefins (Scheme 1). Separation of compounds **5a, 6a** and **5b, 6b** simply could be achieved by means of medium pressure liquid chromatography (yields of pure products: **5a** 59%, **6a** 19%; **5b** 30%, **6b** 48%). When diethyl benzylphosphonate was employed as the Wittig-Horner reagent, also the ketone **3** was transformed into a single isomer **4**. In this case however, the new phenyl substituent and the heteroaromatic ring are in *trans* position as shown by NOE experiments (see below).



Scheme 1

In view of studies aimed towards the preparation of heteroarene congeners of zimeldine [3] [(*Z*)-1-(4-bromophenyl)-3-dimethylamino-1-(3-pyridyl)propene] – a potent antidepressant, which has been withdrawn from the market due to severe side effects – we also tried to react the ketones **1** and **3** with diethyl dimethylaminoethylphosphonate [17] under the conditions successfully applied in the synthesis of compounds **2** and **4**–**6**. This approach, however, failed; likewise attempts to use *n*-butyllithium as deprotonating agent only afforded traces of the olefins **7**, **8**, and **9**.

Wittig-type reactions of **1** or **3** with dimethylaminoethyl triphenylphosphonium bromide/*n*-*Bu*Li, however, were found to permit the desired C=C bond formation. From the ketone **1** we obtained a 3:2 mixture of the *E*/*Z*-isomers **7** and **8**, whereas only one isomer (**9**) could be isolated in the case of ketone **3** (Scheme 2).



Scheme 2 **7** **8** **9**

Configurational Assignments

The determination of the stereochemistry of all novel compounds prepared could be achieved unambiguously by homonuclear NOE difference spectroscopy, which has been widely used for configurational assignment of double bond isomers [18–21]. In the ^{1}H-nmr spectra of all compounds the signal of the alkene-proton is well separated from the signals of aromatic or heteroaromatic protons, thus permitting convenient discrimination between *E* and *Z* isomers as exemplified in Fig. 1.

Irradiation of the alkene-H resonance of the ethyl carboxylate **5b** leads to a marked NOE on the pyridazine H-4, whereas the phenyl-H lines remain unaffected. This clearly indicates *E*-configuration. On the other hand, with compound **6b** *Z*-configuration follows from a positive NOE on the aromatic protons observed upon perturbation of the alkene-H singlet (an NOE on pyridazine H-4 is not observed). These assignments are further confirmed by chemical shift arguments: the alkene-H resonance of **5b** appears at lower field (δ 7.02 ppm) than that of the corresponding isomer **6b** (δ 6.71 ppm). Considering a conformation of **5b** in which the alkene-H is located close to the lone pair of the pyridazine N-2, this can be attributed to an anisotropy effect.

In an analogous manner, the configuration of compounds **5a** and **6a** could be determined. *E*-Configuration of compound **4** clearly follows from the observation that irradiation of the alkene-H line not only affects H-resonances of the geminal phenyl substituent but also leads to a marked enhancement of the signals of pyridazine H-4 [22].

A through-space connection between the alkene-H and phenyl protons observed in NOE difference experiments with compounds **2b** and **2c** (each obtained as the sole product upon reaction of ketone **1** with the appropriate diethyl phosphonate) clearly revealed *Z*-configuration. With compound **2a**, NOE difference spectra had to be recorded at 400 MHz spectrometer frequency, since with low-field spectrometers severe problems owing to overlapping of lines arose. Multiplet irradiation of

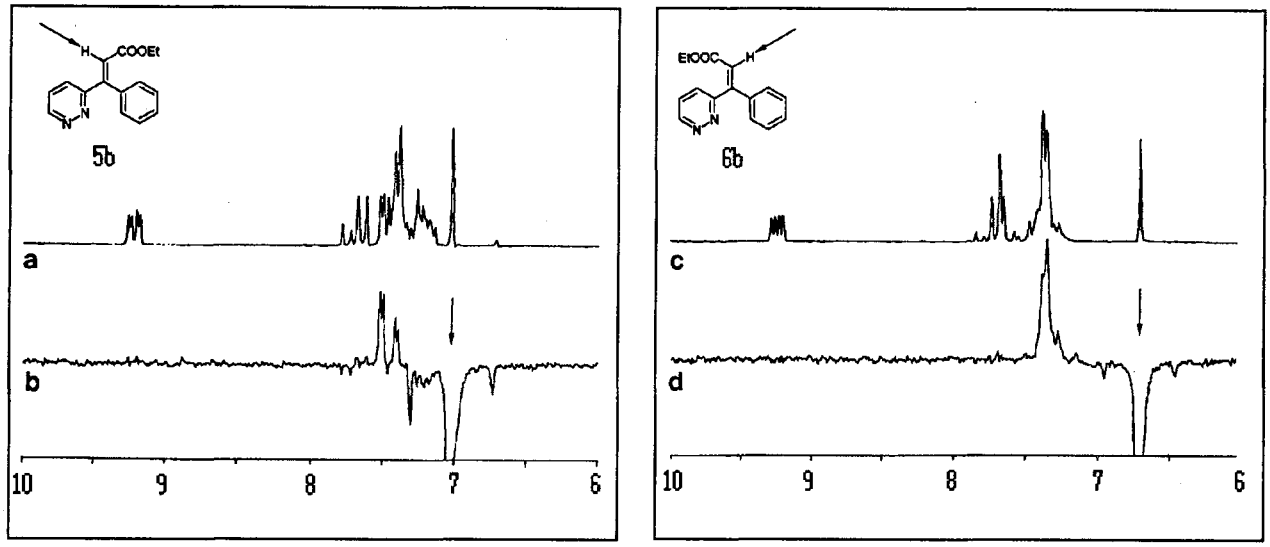


Fig. 1. *a* 80 MHz ^{1}H-nmr spectrum of **5b** (*DMSO-d_6*, 6–10 ppm); *b* NOE difference spectrum of **5b** resulting from irradiation of the alkene-H; *c* 80 MHz ^{1}H-nmr spectrum of **6b** (*DMSO-d_6*, 6–10 ppm); *d* NOE difference spectrum of **6b** resulting from irradiation of the alkene-H

the pyridazine H-3 or H-5 resonances, respectively, enhanced the signals of the *ortho*-protons of both phenyl systems, but not the signal of the alkene-H. In accordance, perturbation of the alkene-H did not influence the pyridazine H-3 or H-5, but again an NOE on benzene H-2/H-6 and H-2′/H-6′ was detected. Thus, also for compound **2a**, *Z*-configuration has to be assigned.

NOE difference experiments with the 3 : 2 mixture of the stereoisomers **7** and **8** allowed to assign *E*-configuration to the main component and thus *Z*-configuration to **8**. Similarly, the effect on pyridazine H-4 upon irradiation of the alkene-H triplet revealed *E*-configuration of the olefine **9**.

Thus, Wittig-Horner carbonyl-olefination reactions of phenyl pyridazinyl ketones were shown to provide convenient access to novel 1-aryl-1-heteroarylethenes of type **2, 4, 5,** and **6**. Also in this series, NOE difference spectroscopy proved to be a powerful tool for the determination of configuration.

Experimental Part

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The glc/ms analyses were carried out on a Hewlett-Packard 5890A/5970B-GC/MSD instrument. The ir spectra (potassium bromide pellets or dichloromethane solution) were recorded on a Jasco IRA-1 spectrometer. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna. Medium pressure liquid chromatography (mplc) was performed using Lobar® glass columns filled with 250 g of LiChroprep® Si-60 (Merck). ^{1}H-nmr specra were recorded from approximately 0.2 *M* solutions at 30°C on a Bruker AC80 spectrometer (80.13 MHz spectrometer frequency) equipped with an Aspect 3000 computer and standard software. Generally used parameters for the acquisition of NOE difference spectra: 8 K data points, spectral width: 1 441 Hz; acquisition time: 2.84 s; digital resolution: 0.35 Hz/point; pulse width: 3 μs (90°); relaxation delay: 0.5 s; number of scans: 160–800; pre-irradiation time: 3–5 s; irradiation power: 48–50 dB below 0.2 W. Multiplet irradiation was carried out using the method of Kinns [23] (irradiation power: 59–61 dB). NOE

difference spectra of compounds **2a** and **9** were recorded on a Bruker AM 400 WB spectrometer (spectrometer frequency: 400.14 MHz). NOE difference spectra displayed in Fig. 1 were processed with 0.5 Hz line broadening to reduce subtraction artifacts. The pyridazine protons always occur as ABX spin-systems with typical coupling constants: 4-substituted pyridazine derivatives: $^4J_{H\text{-}3,\,H\text{-}5} \sim 2.3$ Hz, $^5J_{H\text{-}3,\,H\text{-}6} \sim 1.3$ Hz, $^3J_{H\text{-}5,\,H\text{-}6} \sim 5.3$ Hz; 3-substituted pyridazine derivatives: $^4J_{H\text{-}4,\,H\text{-}6} \sim 1.7$ Hz, $^3J_{H\text{-}5,\,H\text{-}6} \sim 4.8$ Hz, $^3J_{H\text{-}4,\,H\text{-}5} \sim 8.7$ Hz.

Wittig-Horner-Reactions with Phenyl Pyridazinyl Ketones – General Procedure

To a solution of the appropriate phosphonate (1 mmol) in 5 ml of dry dimethylformamide were added 30 mg of sodium hydride (80% suspension in paraffine, 1 mmol) under argon atmosphere. After stirring the mixture for 1 h at room temperature, a solution of 184 mg (1 mmol) of phenyl 4-pyridazinyl ketone (**1**) or of phenyl 3-pyridazinyl ketone (**3**), respectively, in 5 ml of dimethylformamide was added and stirring was continued for 15 h. Then 20 ml of water were added and the mixture was extracted exhaustively with dichloromethane. The residue obtained after evaporation of the combined organic layers was subjected to mplc (eluent: ethyl acetate).

(Z)-1,2-Diphenyl-1-(4-pyridazinyl)ethene (**2a**)

Yield: 180 mg (70%), colorless oil. ^{1}H-Nmr (400 MHz, *DMSO-d*$_6$) $\delta = 9.23$ (dd, 1 H, pyridazine H-6), 8.95 (dd, 1 H, pyridazine H-3), 7.49 (dd, 1 H, pyridazine H-5), 7.42–7.34 (m, 3 H, phenyl H-3,4,5) [24], 7.33 (s, 1 H, olefinic H), 7.31–7.26 (m, 2 H, phenyl H-2,6) [24], 7.24–7.17 (m, 3 H, phenyl H-3′,4′,5′) [24], 7.01–7.04 (m, 2 H, phenyl H-2′,6′) [24]. Ms: $m/z = 258$ (M^+, 100%), 229 (92), 228 (61), 215 (22). $C_{18}H_{14}N_2$ (258.33). Calcd. for $C_{18}H_{14}N_2 \cdot 1.1\,H_2O$: C 77.73, H 5.87, N 10.07; found: C 77.56, H 5.59, N 10.24.

(Z)-3-Phenyl-3-(4-pyridazinyl)propenenitrile (**2b**)

Yield: 130 mg (63%), pale yellow crystals (from cyclohexane), m.p. 130–131°C. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.44$ (dd, 1 H, pyridazine H-6), 9.27 (dd, 1 H, pyridazine H-3), 7.79 (dd, 1 H, pyridazine H-5), 7.54–7.34 (m, 5 H, phenyl-H), 6.70 (s, 1 H, olefinic H). IR (CH_2Cl_2): 2190 cm^{-1} (C≡N). Ms: $m/z = 207$ (M^+, 100%), 178 (56), 152 (36), 151 (31). $C_{13}H_9N_3$ (207.24). Calcd.: C 75.35, H 4.38, N 20.28; found: C 75.55, H 4.24, N 20.22.

(Z)-Ethyl 3-Phenyl-3-(4-pyridazinyl)propenoate (**2c**)

Yield: 220 mg (87%), colorless crystals (from cyclohexane), m.p. 75–76°C. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.28$ (dd, 1 H, pyridazine H-6), 9.09 (dd, 1 H, pyridazine H-3), 7.54 (dd, 1 H, pyridazine H-5), 7.49–7.28 (m, 5 H, phenyl-H), 6.68 (s, 1 H, olefinic H), 3.99 (q, $J = 7.1$ Hz, 2 H, OCH_2), 1.06 (t, $J = 7.1$ Hz, 3 H, CH_3). Ir (CH_2Cl_2): 1690 cm^{-1} (C=O). Ms: $m/z = 254$ (M^+, 5%), 225 (72), 197 (100), 153 (32), 141 (38). $C_{15}H_{14}N_2O_2$ (254.29). Calcd.: C 70.85, H 5.55, N 11.02; found: C 70.77, H 5.41, N 11.05.

(E)-1,2-Diphenyl-1-(3-pyridazinyl)ethene (**4**)

Yield: 115 mg (45%) [25], colorless oil. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.14$ (dd, 1 H, pyridazine H-6), 7.83 (s, 1 H, olefinic H), 7.62 (dd, 1 H, pyridazine H-5), 7.49–7.08 (m, 6 H, phenyl-H, pyridazine H-4). Ms: $m/z = 258$ (M^+, 30%), 257 (100). $C_{18}H_{14}N_2$ (258.33). Calcd. for $C_{18}H_{14}N_2 \cdot \frac{1}{4}\,H_2O$: C 82.26, H 5.56, N 10.66; found: C 82.03, H 5.54, N 11.04.

(E)-3-Phenyl-3-(3-pyridazinyl)propenenitrile (**5a**)

Yield: 122 mg (59%), almost colorless crystals (from cyclohexane), m.p. 136°C. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.30$ (dd, 1 H, pyridazine H-6), 7.78 (m, 1 H, pyridazine H-5), 7.62 (m, 1 H, pyridazine H-4), 7.61–7.35 (m, 5 H, phenyl-H), 6.87 (s, 1 H, olefinic H). Ir (KBr): 2 200 cm^{-1} (C≡N). Ms: $m/z = 207$ (M^+, 38%), 206 (100), 181 (20). $C_{13}H_9N_3$ (207.24). Calcd.: C 75.35, H 4.38, N 20.28; found: C 75.22, H 4.40, N 20.34.

(E)-Ethyl 3-Phenyl-3-(3-pyridazinyl)propenoate (**5b**)

Yield: 75 mg (30%), colorless oil. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.22$ (dd, 1 H, pyridazine H-6), 7.69 (m, 1 H, pyridazine H-5), 7.48 (m, 1 H, pyridazine H-4), 7.45–7.12 (m, 5 H, phenyl-H), 7.02 (s, 1 H, olefinic H), 3.99 (q, $J = 7.1$ Hz, 2 H, OCH_2), 1.02 (t, $J = 7.1$ Hz, 3 H, CH_3). Ir (CH_2Cl_2): 1 710 cm^{-1} (C=O). Ms: $m/z = 253$ ($M^+ - 1$, 9%), 225 (100), 181 (40). $C_{15}H_{14}N_2O_2$ (254.29). Calcd.: C 70.85, H 5.55, N 11.02; found: C 70.61, H 5.45, N 11.29.

(Z)-3-Phenyl-3-(3-pyridazinyl)propenenitrile (**6a**)

Yield: 39 mg (19%), colorless oil. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.34$ (dd, 1 H, pyridazine H-6), 7.95–7.71 (m, 2 H, pyridazine H-5, H-4), 7.56–7.37 (m, 5 H, phenyl-H), 6.46 (s, 1 H, olefinic H). Ir (KBr): 2 210 cm^{-1} (C≡N). Ms: $m/z = 207$ (M^+, 42%), 206 (100), 181 (21). $C_{13}H_9N_3$ (207.24). Calcd.: C 75.35, H 4.38, N 20.28; found: C 75.49, H 4.64, N 20.12.

(Z)-Ethyl 3-Phenyl-3-(3-pyridazinyl)propenoate (**6b**)

Yield: 121 mg (48%), colorless oil. ^{1}H-Nmr (80 MHz, *DMSO-d*$_6$) $\delta = 9.24$ (dd, 1 H, pyridazine H-6), 7.85–7.55 (m, 2 H, pyridazine H-4, H-5), 7.38–7.27 (m, 5 H, phenyl-H), 6.71 (s, 1 H, olefinic H), 3.94 (q, $J = 7.1$ Hz, 2 H, OCH_2), 1.01 (t, $J = 7.1$ Hz, 3 H, CH_3). Ir (KBr): 1 695 cm^{-1} (C=O). Ms: $m/z = 253$ ($M^+ - 1$, 8%), 225 (100), 181 (32). $C_{15}H_{14}N_2O_2$ (254.29). Calcd. for $C_{15}H_{14}N_2O_2 \cdot \frac{1}{4} H_2O$: C 69.62, H 5.65, N 10.82; found: C 69.67, H 5.50, N 11.14.

Reaction of **1** *and* **3** *with 2-Dimethylaminoethyl Triphenylphosphonium Bromide*

To a cooled (0°C) suspension of 207 mg (1 mmol) of 2-dimethylaminoethyl triphenylphosphonium bromide in 10 ml of dry tetrahydrofuran were added dropwise 0.75 ml (1.2 mmol) of a 1.6 *N* solution of *n*-butyllithium in *n*-hexane under argon atmosphere. The mixture was stirred for 30 min and then a solution of 184 mg (1 mmol) of **1** or **3**, respectively, in 5 ml of tetrahydrofuran was added within 5 min. The mixture was allowed to warm up to room temperature and stirring was continued for 1 h. Then the solvents were evaporated in vacuo and the residue was subjected to column chromatography (Kieselgel 60, 70–230 mesh ASTM, Merck; gradient-elution: gradient ethyl acetate → methanol → water). The fraction containing the most retarded component was evaporated and the residue was extracted with acetone. Thus, after removal of acetone, were obtained starting from ketone **1** 110 mg (46%) of a mixture of **7** and **8**: pale yellow oil. ^{1}H-Nmr (80 MHz, acetone-*d*$_6$) $\delta = 9.28$–9.03 (m, pyridazine H-3, H-6 of **7** and **8**), 7.53–7.15 (m, pyridazine H-5 and phenyl-H of **7** and **8**), 6.65 (t, $J = 6.7$ Hz, olefinic H of **7**), 6.41 (t, $J = 6.9$ Hz, olefinic H of **8**), 3.01 (d, $J = 6.7$ Hz, CH_2 of **7**), 2.96 (d, $J = 6.9$ Hz, CH_2 of **8**), 2.18 (s, methyl-H of **7** and **8**). Glc/ms: **7**: $m/z = 239$ (M^+, 29%), 238 (81), 196 (63), 160 (60), 152 (40), 115 (32), 91 (36), 70 (38), 58 (100); **8**: $m/z = 239$ (M^+, 18%), 238 (58), 196 (91), 195 (33), 167 (100), 165 (60), 160 (82), 152 (49), 58 (90). $C_{15}H_{17}N_3$ (239.32). Calcd.: C 75.28, H 7.16, N 17.56; found: C 75.12, H 6.86, N 17.32.

Use of the ketone **3** as educt afforded 45 mg (19%) of **9**, colorless oil. ^{1}H-Nmr (400 MHz, acetone-*d*$_6$) $\delta = 9.06$ (dd, 1 H, pyridazine H-6), 7.53 (dd, 1 H, pyridazine H-5), 7.48–7.39 (m, 3 H, phenyl H-3,4,5), 7.27–7.23 (m, 3 H, pyridazine H-4, phenyl H-2,6), 7.03 (t, $J = 6.8$ Hz, 1 H, olefinic H), 3.02

(d, $J=6.8$ Hz, 2 H, CH_2), 2.18 (s, 6 H, CH_3). Ms: $m/z=239$ (M^+, 43%), 196 (73), 195 (100), 191 (43), 58 (26). $C_{15}H_{17}N_3$ (239.32). Calcd.: C 75.28, H 7.16, N 17.56; found: C 75.10, H 6.84, N 17.36.

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