Synthesis of Azinylvinylpyridazines: A General Note on the Isomerization of Hetaryldienamines†

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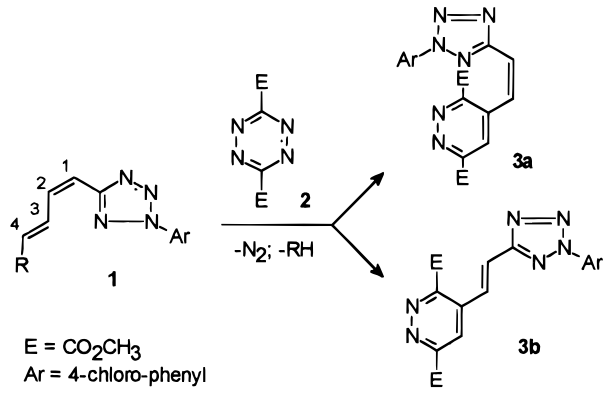
Azinyldienamines underwent Diels Alder reaction of inverse electron demand with 1,2,4,5-tetrazine diester to give azinylvinylpyridazines. Comparison of the products obtained from mono-, di-, and triazinyldienamines revealed that, in some cases, isomerization of the olefinic side chain occurred which can be rationalized by the tautomeric conditions of the intermediates bearing these azine moieties. These experimental findings supported also by semiempirical calculations suggest the importance of the influence of the hetaryl group in such isomerizations.

Recently we have found[1] that azolyldienes (*e.g.* the **1**) when reacted with tetrazine 1,4-dicarboxylic ester **2** undergo Diels−Alder reaction of inverse electron demand with participation of one of the diene double bonds (*i.e.* with Δ3,4) to yield pyridazines (*e.g.* **3a** or **3b**) bearing an azolylvinyl side chain.

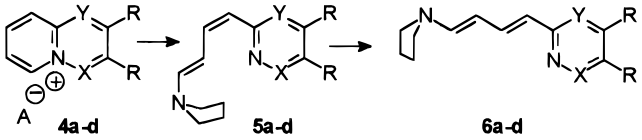
This side chain in the products generally conserved the geometry of the Δ1,2 bond of the starting compound, *i.e.* the 1-*cis* diene **1** normally afforded **3a**. The observation that in special cases the starting diene **1** (*e.g.* when R = OCH_3) led to **3b** having a *trans* external double bond was interpreted by the tautomeric behavior of an intermediate of the reaction path having a dienamine substructure. This unexpected finding directed our attention to a more thorough investigation of cycloadditions of this type.

In addition to our ongoing studies on azolyldienes we now decided to investigate the analogous reactions of azinyldienes as well. On this class of compounds only very little work has been published in the literature: Kröhnke et al.[2] described first the ring opening of the quinolizinium salt **4a** to the *trans-trans* pyridyldiene **6a**, and later also some other reports appeared in this field[3−6] which concluded that the reaction of the azinium salt with secondary amines proceeds through the salt → *cis-trans* dienamine → *trans-trans* dienamine (*i.e.* **4** → **5** → **6**) sequence. Based on our earlier experience on analogous ring opening reactions,[7] this methodology has now been extended to study the ring opening of the diphenyl derivative **4b** by pyrrolidine as well as ring opening of the pyridopyridazinium salt **4c** and of the pyrido[1,2-*b*]-[1,2,4]triazinium salt **4d** by the same reagent. The appropriate starting azinium salts **4b** and **4d** were obtained according to literature procedures[8−10] whereas

Scheme 1



Scheme 2



a: X=CH, Y=CH, R=H; **b**: X=CH, Y=CH, R=Ph;
c: X= N, Y=CH, R=Ph; **d**: X=N, Y=N, R=Ph

4c was synthesized upon analogy of the method of Alvarez-Builla.[11]

As the geometry of the resulting azinyldienes was of especial importance from the point of view of the desired cycloadditions, we made serious efforts in order to isolate both 1-*trans*-3-*trans* **6** and 1-*cis*-3-*trans* products **5**. Although the existence of **5** as the primary product in such ring openings has been proved by NMR spectroscopy,[3−5] in most cases only the more stable 1-*trans*-3-*trans* isomer **6** could be isolated so far.

In accord with these earlier literature findings we experienced, indeed, that in ring openings of all three selected model systems **4b**−**d**, 1-*cis*-3-*trans* dienes **5b**−**d** were formed first which in the presence of protic solvents underwent a rapid isomerization to the *trans-trans* products **6b**−**d**. By proper choice of the reaction conditions, however (by using absolute acetonitrile as a

† Cordially dedicated to Prof. M. Tišler on the occasion of his 70th birthday.

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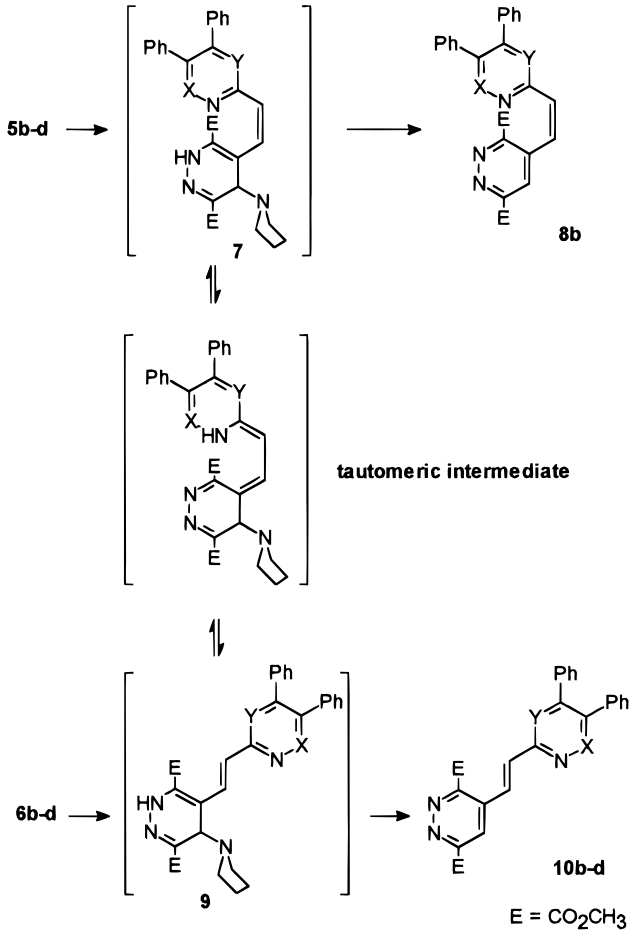
Scheme 3



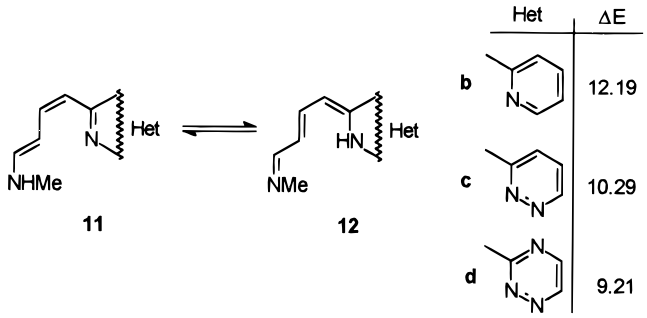
b: X=CH, Y=CH; **c**: X= N, Y=CH; **d**: X=N, Y=N

solvent), the primary products 1-*cis*-3-*trans* dienes **5b**−**d** could also be isolated in crystalline form.

All the three diphenylazinyl-substituted 1-*trans*-3-*trans* dienes **6b**−**d** underwent a facile cycloaddition with tetrazine diester and afforded, as expected, the corresponding *trans*-azinylvinylpyridazines **10b**−**d**. Interestingly, however, the three 1-*cis*-3-*trans* azinyldienes **5b**−**d**, furnished different products: ^{1}H-NMR analysis revealed that only the product **8b** obtained from **5b** conserved the original *cis* geometry of the side chain, whereas the other two model compounds **5c**,**d** afforded the same *trans* products **10c**,**d** which were also obtained from the fully *trans* isomers as described above. As our recent observation with the the related azolyldienes[1] suggested that such isomerization may be due to the tautomeric equilibria of the intermediates, analysis of the tautomeric conditions of these structures seemed to be straightforward.

On the analogy of the cycloaddition reactions of azolyldienamines,[1] the two isomeric azinyldienamine **5** and **6** should afford the intermediates **7** and **9**, respectively. In the cases where the 1-*cis*-3-*trans* azinyldiene led to a *trans* final product (*i.e.* with **5c** or **5d** which gave **10c** and **10d**, respectively) an equilibrium between **7c**,**d** and **9c**,**d** should be anticipated which is considerably facilitated by formation of a "tautomer intermediate" (Scheme 3). The above finding, however, that this isomerization takes only place with the intermediates **7c** and **7d** formed from the pyridazinyl and triazinyldienes (**5c** and **5d**) and cannot be observed with the related pyridyl analogue **7b**,

Chart 1. Calculated Differences in the Heats of Formation (kcal/mol) of the Tautomeric Structures 11 and 12 ($\Delta E = \Delta_f H$ (12) − $\Delta_f H$ (11), PM3, MOPAC 6.0)



can only be explained by this mechanism if an explanation can be found for the different extent of the equilibric shift for the three model azine rings.

We have carried out calculations in order to assess the ease of tautomerization facilitating the observed isomerization. As a model system a series of hetaryl(methylamino)dienes **11** and their tautomers **12** have been selected and the differences between the heats of formation (PM3 method[12]) of these structure pairs (ΔE) have been compared. The results are shown in Chart 1 and seem to be in satisfactory agreement with the experimental finding: in the pyridine case the shift of the equilibrium from **11b** to **12b** is essentially less probable than the cases of the diazinyl and triazinyl dienes which can furnish the tautomers **12c** and **12d** with a lower energy investment.

The fact that in polyazines the substructure containing an exo double bond is energetically relatively more favorable than in the monoazine may provide a general rationale for the so far not yet interpreted experimental data found with isomerizations of 1-*cis* hetaryldienamines to the 1-*trans* isomers (*e.g.* **5** to **6**) as listed below:

(i) Under aprotic conditions no isomerization occurs.[13,14]

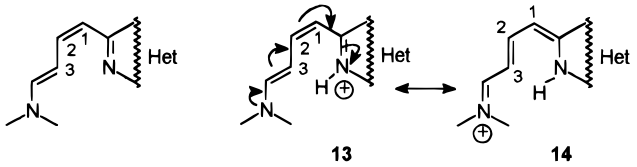
(ii) 1-Tetrazolyl-4-alkoxydienes as well as 1-tetrazolyl-4-aziridinyldienes do not undergo isomerization even under forced conditions.[14]

(iii) In the course of this study we observed that 1-*cis*-3-*trans*-tetrazolyldienamines and triazinyldienamines can be prepared in pure state only by a special technique; otherwise these compounds spontaneously undergo a very rapid isomerization to the fully trans isomers. The related 1-*cis*-3-*trans*-pyridyldienamine, in turn, is quite stable and can be stored for several weeks without any isomerization.

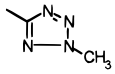
Finding i suggests that the isomerization proceeds *via* a protonation step or formation of a hydrogen bond by solvatation and because of finding ii the conjugation of the lone pair of the terminal substituent of the diene chain is necessary for the success of the process.[15] Thus, a mechanism involving a protonated intermediate represented by the mesomeric structures **13** and **14** as shown in Chart 2 seems to be convincing which suggests that the bond order of Δ1,2 can sufficiently be decreased as a consequence of the shifts of electrons increasing the

(12) Stewart, J. J. P.; *J. Comput. Chem.* **1989**, *10*, 209.
(13) Gelléri, A.; Messmer, A. *Tetrahedron Lett.* **1973**, *14*, 4295.
(14) Messmer, A.; Hajós, Gy.; Timári, G. *Tetrahedron*, **1992**, *48*, 8451.
(15) The unavailibity of the lone pair of aziridine-nitrogen atom for delocalization is well documented; *e.g.* Johnson, J. E.; Maia, A. K. *J. Heterocycl. Chem.* **1986**, *23*, 1861.

Chart 2. Calculated C1−C2 and C2−C3 Bond Length Values (in angstroms) of the Equilibrium Geometries of the Neutral (A) and Protonated (B) Hetaryl(dimethylamino)butadienes (PM3, MOPAC 6.0)



NEUTRAL FORM (A) PROTONATED FORM (B)

	Het:				
A	C1-C2	1.34	1.34	1.34	1.34
	C2-C3	1.45	1.44	1.44	1.44
B	C1-C2	1.37	1.38	1.39	1.41
	C2-C3	1.41	1.40	1.39	1.38

contribution of the mesomeric structure **14**. An alternative mechanism for this isomerization implying the protonation of C-1 of the diene chain as found by Katritzky[16] in a special related case (with isoxazolinyl derivatives) could be ruled out by the following experiment: the *cis-trans* dienamine (*e.g.* **5b**) was isomerized in CD_3OD to the *trans-trans* isomer **6b** whereupon no incorporation of deuterium into the diene chain under these experimental conditions was observed.

According to this mechanistic picture, furthermore, finding iii could also be rationalized if the extent of the contribution of mesomeric structure **14** significantly depends on the heteroaromatic substituent. The calculated bond lengths as shown in Chart 2 seem to support this hypothesis.

Chart 2 summarizes the calculated bond lengths of the protonated intermediates ("form B" represented by valence bond structures **13** and **14**) compared to the neutral dienes ("form A") and convincingly shows that in form A all Δ1,2 bonds have a double bond character whereas the lengths of the Δ2,3 bonds are close to those of a single bond. In form B, however, the values for Δ1,2 and Δ2,3 approach to each other considerably indicating the increasing conjugation (*i.e.* the importance of the valence bond structure **14**). Comparison of the data of the two experimentally found extremes: the pyridine and tetrazole derivatives, on the other hand, reveals that in the pyridyl compound Δ1,2 almost conserved its double bond character (very slow isomerization was found), whereas in the tetrazolyldiene the length of this bond exceeded that of Δ2,3. In classical terms, contribution of the valence bond structure **14** became more important in this latter case which seems to be in a nice agreement with the experienced very facile isomerization.

Experimental Section[17]

3,4-Diphenylpirido[2,1-*f*]pyridazinium Perchlorate (4c). A solution of 1-amino-2-methylpyridinium tosylate (10.0 g, 36 mmol), benzil (8.4 g, 40 mmol), and triethylamine (4.2 g, 42 mmol) in acetonitrile (80 mL) was refluxed for 2 h. After cooling the precipitate was filtered and dissolved in 70 mL of 15% ethanol, and after the addition of 60% perchloric acid, the precipitated perchlorate salt was filtered off and recrystallized from acetonitrile. yield: 10.15 g (74%); mp 233−35 °C; UV (MeOH) 286, 326 nm; IR 1629, 1461, 1389, 1096, 924 cm^{-1}; ^1H NMR (60 MHz, TFA) J = 7.0 Hz, 1H), 8.61 (d, J = 7.1 Hz, 1H), 8.55 (s, 1H), 8.23 (m, 1H), 7.62−7.24 (m, 11H). Anal. Calcd for $C_{12}H_{15}N_2O_4Cl$: C, 62.75; H, 3.95; N, 7.32. Found: C, 62.92; H, 3.89; N, 7.50.

Synthesis of the New 1*Z*,3*E*-Butadienes 5b-d. To a solution of the appropriate azinium salt **4** (5 mmol) in absolute acetonitrile (5 mL) was added pyrrolidine (2mL) dropwise at 0 °C. The mixture was stirred for 1 h and left standing in a refrigerator overnight. The precipitated crude dienamines were filtered off and recrystallized from acetonitrile.

3,4-Diphenyl-6-[4-(pyrrolidin-1-yl)buta-(1*Z*,3*E*)-1,3-dienyl]pyridine (5b): yield 64%; mp 161−163 °C (CH_3CN); UV (MeOH) 268, 400 nm; IR 1622, 1577, 1466, 1250, 1097, 982, 924 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) J = 11.0 Hz, 1H), 7.55−7.10 (m, 12H), 6.72 (dd, J = 13.0, 11.0 Hz, 1H), 6.58 (d, J = 13.0 Hz, 1H), 5.90 (d, J = 11.0 Hz, 1H), 3.23 (m, 4H), 1.88 (m, 4H). Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 84.94; H, 6.94; N, 8.05.

3,4-Diphenyl-6-[4-(pyrrolidin-1-yl)buta-(1*Z*,3*E*)-1,3-dienyl]pyridazine (5c): yield 82%; mp 139−142 °C (CH_3CN); UV (MeOH) 278, 414 nm; IR 1618, 1564, 1444, 1242, 1089, 973, 914 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) J = 11.0 Hz, 1H), 7.45−7.15 (m, 11H), 6.75 (dd, J = 13.0, 11.0 Hz, 1H), 6.61 (d, J = 13.0 Hz, 1H), 5.91 (d, J = 11.0 Hz, 1H), 3.18 (m, 4H), 1.80 (m, 4H). Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.40; H, 6.57; N, 11.81.

5,6-Diphenyl-3-[4-(pyrrolidin-1-yl)buta-(1*Z*,3*E*)-1,3-dienyl]-*as*-triazine (5d): yield 85%; mp 132−135 °C (CH_3CN); UV (MeOH) 290, 412 nm; IR 1621, 1500, 1462, 1242, 1060, 992, 924 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) J = 7.5 Hz,2H), 7.55 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 11.0 Hz, 1H), 7.40−7.26 (m, 6H), 6.83 (dd, J = 13.0, 11.0 Hz, 1H), 6.72 (d, J =11.0 Hz, 1H), 6.46 (d, J = 13.0 Hz, 1H), 3.37 (m, 4H), 1.95 (m, 4H). Anal. Calcd for $C_{23}H_{22}N_4$: C, 77.93; H, 6.26; N, 15.81. Found: C, 77.77; H, 6.14; N, 15.66.

Synthesis of the New 1*E*,3*E*-Butadienes 6b-d. These compounds were prepared similarly as described above for **5b−d** with the difference that 80% ethanol was used as a solvent.

3,4-Diphenyl-6-[4-(pyrrolidin-1-yl)buta-(1*E*,3*E*)-1,3-dienyl]pyridine (6b): yield 70%; mp 128−130 °C (CH_3CN); UV (MeOH) 398 nm; IR 1623, 1580, 1466, 1280, 1097, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 15.0, 11.0 Hz, 1H), 6.77 (d, J = 13.0 Hz, 1H), 6.28 (d, J = 15.0 Hz, 1H), 5.22 (dd, J = 13.0, 11.0 Hz, 1H), 3.23 (m, 4H), 1.88 (m, 4H). Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 84.99; H, 6.90; N, 8.07.

3,4-Diphenyl-6-[4-(pyrrolidin-1-yl)buta-(1*E*,3*E*)-1,3-dienyl]pyridazine (6c): yield 60%; mp 127−130 °C (CH_3CN); UV (MeOH) 276, 398 nm; IR 1620, 1596, 1560, 1440, 1275, 1218, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 13.0 Hz, 1H), 6.28 (d, J = 15.0 Hz, 1H), 5.15 (dd, J = 13.0, 11.0 Hz, 1H), 3.18 (m, 4H), 1.80 (m, 4H). Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.36; H, 6.54; N, 11.84.

5,6-Diphenyl-3-[4-(pyrrolidin-1-yl)buta-(1*E*,3*E*)-1,3-dienyl]-*as*-triazine (6d): yield 68%; mp 130−133 °C (CH_3CN); UV (MeOH) 290, 412 nm; IR 1622, 1593, 1503, 1412, 1280, 1134, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 15.0, 11.0 Hz, 1H), 6.40 (d, J = 15.0 Hz, 1H), 5.23 (dd, J = 13.0, 11.0 Hz, 1H), 3.37 (m, 4H), 1.95 (m, 4H). Anal. Calcd for $C_{23}H_{22}N_4$: C, 77.93; H, 6.26; N, 15.81. Found: C, 77.72; H, 6.10; N, 15.89.

Reaction of the Dienamines 5b−d and 6b−d and Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate (2). The appropriate dienamine (1 mmol) was added in portions to a solution of the tetrazine reagent **2** (1 mmol) in acetonitrile (3 mL). The mixture was stirred at room temperature for 3 h, and than the precipitated crude product was filtered off and recrystallized from the appropriate solvent.

(16) Eisenthal, R.; Katritzky, A. R.; Lunt, E. *Tetrahedron* **1967**, *33*, 2775.

(17) Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded as KBr discs with a Nicolet 205 FT apparatus. The NMR spectra were registered on Varian XL-400 equipment using $CDCl_3$ as solvent and TMS as an internal standard.

4-{(*Z*)-2-[4,5-Diphenylpyridin-2-yl]vinyl}pyridazine-3,6-dicarboxylic Acid Dimethyl Ester (8b). This compound was prepared from **5b**: yield 28%; mp 122−125 °C (toluene); UV (MeOH) 248, 314 nm; IR 1731, 1585, 1441, 1269, 1134, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 12.5 Hz, 1H), 7.27−7.22 (m, 6H), 7.10−7.05 (m, 4H), 6.96 (d, J = 12.5 Hz, 1H), 4.13 (s, 3H), 4.09 (s, 3H) (s, 3H). Anal. Calcd for $C_{27}H_{21}N_3O_4$: C, 71.67; H, 4.90; N, 9.29. Found: C, 71.55; H, 4.86; N, 9.45.

4-{(*E*)-2-[4,5-Diphenylpyridin-2-yl]vinyl}pyridazine-3,6-dicarboxylic Acid Dimethyl Ester (10b). This compound was prepared from **6b**: yield 56%; mp 153−156 °C (toluene); UV (MeOH) 248, 312 nm; IR 1733, 1585, 1440, 1268, 1134, 995, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 16.0 Hz, 1H), 7.60 (d, J = 16.0 Hz, 1H), 7.53 (s, 1H), 7.27−7.22 (m, 6H), 7.10−7.05 (m, 4H), 4.13 (s, 3H), 4.12 (s, 3H). Anal. Calcd for $C_{27}H_{21}N_3O_4$: C, 71.67; H, 4.90; N, 9.29. Found: C, 71.39; H, 5.10; N, 9.41.

4-{(*E*)-2-[3,4-Diphenylpyridazin-6-yl]vinyl}pyridazine-3,6-dicarboxylic Acid Dimethyl Ester (10c). This compound was prepared from **5c**: yield 35%; mp 180−183 °C (toluene); UV (MeOH) 216, 294 nm; IR 1730, 1580, 1440, 1270, 1135, 1000, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) J = 16.0 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.73 (s, 1H), 7.49 (d, J = 7.5 Hz, 2H), 7.40−7.30 (m, 6H), 7.26 (d, J = 7.5 Hz, 2H), 4.11 (s, 3H), 4.10 (s, 3H). Anal. Calcd for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.90; H, 4.52; N, 12.25.

5,6-Diphenyl-3-{(*E*)-2-[3,6-(bis(methoxycarbonyl)pyridazin-4-yl]vinyl}-*as*-triazine (10d). This compound was prepared from **5d** yield 40%; mp 205−207 °C (toluene); UV (MeOH) 292 nm; IR 1738, 1579, 1450, 1260, 1142, 979 cm^{-1}; $_1H$ NMR (400 MHz, $CDCl_3$) J = 16.0 Hz, 1H), 8.62 (s, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.50−7.37 (m, 6H), 4.00 (s, 3H), 3.95 (s, 3H). Anal. Calcd for $C_{25}H_{19}N_5O_4$: C, 66.22; H, 4.22; N, 15.44. Found: C, 66.25; H, 4.36; N, 15.24.

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