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Unequivocal Determination of Isomeric Products of Reaction between 3-Methyl-1-phenyl-2-pyrazoline-4,5-dione and Aromatic 1,2-Diamines

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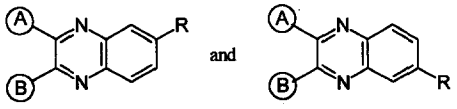
Abstract: Regioselectivity of condensation of 3-methyl-1-phenyl-2-pyrazoline-4,5-dione with aromatic 1,2-diamines is dependent on substituent present. Isomeric 3-methyl-1-phenyl-1*H*-pyrazolo-[3,4-*b*]-quinoxaline products are distinguished by comparison of their 2D *z*-gradient selected $^{1}H,^{15}N$ HMBC (Heteronuclear Multiple Bond Correlation) spectra. Multiplicity of H5 signal, which is recognizable by the cross-peak for CH_3(3)-N4 and H5-N4 interactions, indicates substitution in position 6 or 7. The applied method is expected to be useful for structure determinations in other positional isomers.

INTRODUCTION

Reaction of 3-methyl-1-phenyl-2-pyrazoline-4,5-dione with aromatic 1,2-diamines, *o*-phenylenediamine and 2,3-diaminopyridine, gives 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **1** and its 8-aza analogue, *i.e.* 3-methyl-1-phenyl-1*H*-1,2,4,8,9-pentaazacyclopenta[*b*]naphthalene **9**, respectively.[1] However, the regioselectivity of this reaction was not studied earlier and formation of 3-methyl-1-phenyl-1*H*-1,2,4,5,9-pentaazacyclopenta[*b*]naphthalene **10** from the same substrates should also be considered.[1] To determine the ratio of two isomeric products, one must know how to distinguish them. Problem to be discussed refers to differentiation between two very similar positional isomers



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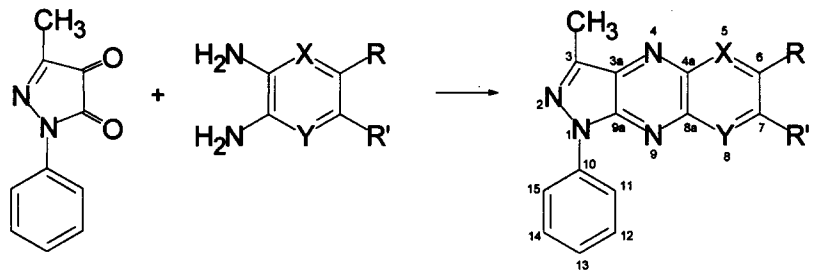
Recently Martin *et al.*[2] used the long-range ^{1}H-^{15}N GHNMQC two-dimensional NMR spectra to locate the *N*-oxidation site in some oxazolidine antibiotics. This method seemed very interesting from the point of view of the structure determination for numerous nitrogen compounds.

RESULTS AND DISCUSSION

Two different products can be formed by condensation of two substrates, each of which contains two different reaction centres. Thus, 6- and 7-substituted 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalines **2–5** and **7–10** were obtained from 3-methyl-1-phenyl-2-pyrazoline-4,5-dione and unsymmetrically substituted aromatic 1,2-diamines (see Experimental).



1 – 10

	X	Y	R	R'		X	Y	R	R'
1	CH	CH	H	H	**6**	CH	CH	Cl	Cl
2	CH	CH	Me	H	**7**	CH	CH	NO_2	H
3	CH	CH	H	Me	**8**	CH	CH	H	NO_2
4	CH	CH	Cl	H	**9**	CH	N	H	H
5	CH	CH	H	Cl	**10**	N	CH	H	H

Some of these compounds show antibacterial activity[3] and are expected to be efficient polymerization photoinitiators and singlet oxygen sensitizers.[4-6] When looking for a suitable method of distinguishing between the isomeric reaction products, we found that homonuclear 2D (^{1}H,^{1}H) ROESY spectra (rotating frame NOESY, a method based on proton-proton dipolar relaxation through space) show only intra-ring interactions. Since the cross-peaks for inter-ring interactions were not observed, such spectra are useless for solving the problem. On the other hand, heteronuclear 2D *z*-gradient selected ^{1}H,^{15}N HMBC (Heteronuclear Multiple Bond Correlation) spectra[7] for compounds **2**, **4**, **6** and **7**, where the signal of H5 is a singlet, show the cross-peaks for C**H**$_3$(3)-N4 and H5-N4 interactions. As the signals of H5 in the spectra of compounds **1**, **3**, **5** and **8** are doublets, it was very

easy to differentiate between these two types of reaction products. Usually separation of H and N atoms by more than four bonds makes HMBC measurements ineffective but occasionally some long-range H-N interactions can be observed. When the delay for their evolution is to long, the whole magnetization could relax during the pulse and this causes only an enormous T_1-noise ridge along ^{15}N -axis. A 100 ms delay in the pulse sequence for evolution of long-range couplings between nitrogen and proton was found optimal for 5 Hz scalar coupling. An illustrative $^{1}H,^{15}N$ HMBC spectrum in Figure 1 shows the cross-peaks including that for the interaction between N1 and H6 separated by seven bonds.

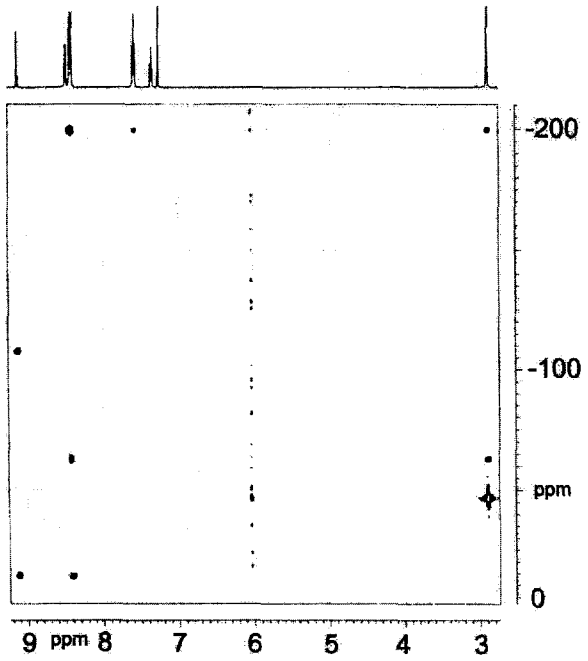


Figure 1. *z*-GS $^{1}H,^{15}N$ HMBC spectrum of compound **8**.

It can be seen that *z*-GS $^{1}H,^{15}N$ HMBC spectra can be very useful for the structure determination of numerous positional isomers that contain nitrogen atom(s). Unfortunately, some cross-peaks are not seen in the spectra of compounds **9** and **10**, so other, yet more sophisticated methods should be used to distinguish rigorously between these two isomeric products.

^{1}H, ^{13}C and ^{15}N NMR chemical shifts for compounds **1–10** shown in Tables 1 and 2 can also give some support to the results obtained using the $^{1}H,^{15}N$ HMBC method. Without going into details, one can see from these data that δ values, when related to the Hammett σ constants, follow the substituent electronic effects. Both ^{1}H NMR and UV-vis spectra can be helpful to determine the product ratio. The data in Table 3 show that the

Table 1. ^{15}N (ppm) and ^{1}H chemical shifts (δ, from ext. CH_3NO_2 and int. TMS, respectively) for compounds **1–10** in $CDCl_3$ at 30°C[a]

	N1	N2	N4	N9	H5	H6	H7	H8
1	-201.2	-54.8	-65.8	-112.1	8.26	7.72	7.81	8.17
2[b]	-201.2	-56.1	-68.7	-112.4	8.02	-	7.66	8.07
3[c]	-201.2	-57.0	-67.1	-114.2	8.16	7.59	-	7.98
4	-200.6	-52.6	-66.9	-111.9	8.25	-	7.75	8.11
5	-200.7	-53.5	-65.0	d	8.22	7.69	-	8.23
6	-200.4	-51.4	-66.0	-114.7	8.41	-	-	8.36
7[e]	-199.4	-48.6	d	-114.2	9.24	-	8.60	8.33
8[f]	-200.0	-47.4	-63.2	-108.0	8.42	8.48	-	9.12
9[g]	-197.9	-47.8	d	-68.3	-	9.28	8.66	7.73
10[g]	-198.4	-47.8	d	-63.8	7.79	8.58	9.24	-

[a] Chemical shifts of other hydrogen atoms [in ppm]: CH_3(3) [2.85–2.92], H11 and H15 [8.39–8.51], H12 and H14 [7.56–7.59], H13 [7.28–7.36]; [b,c] The chemical shifts of CH_3(6) and CH_3(7) are 2.62 and 2.65 ppm, respectively; [d] Not observed; [e,f] The chemical shifts of the nitro nitrogen atoms are -14.4 and -14.5 ppm, respectively; [g] Signals of N8 and N5 were not observed.

regioselectivity is comparable for methyl and chloro derivatives but reversed for the nitro derivatives **7** and **8**. The calculated electron densities at the amino nitrogen atoms in 4-methyl- and 4-chloro-1,2-diaminobenzenes show nucleophilicity of both amino groups to be comparable. On the other hand, the amino group in position *meta* with respect to the nitro group in 4-nitro-1,2-diaminobenzene and that in position 3 in 2,3-diaminopyridine are expected to be more reactive. Thus, the calculated electron densities differentiate two amino groups present in the molecule of the substrate and, to some extent, support formation of the isomeric products in ratios shown in Table 3.

Table 2. ^{13}C chemical shifts (δ, from int. TMS) for compounds **1–10** in $CDCl_3$ at 30°C[a]

	C3a	C4a	C5	C6	C7	C8	C8a	C10
1	137.78	140.77	130.21	128.87	130.82	129.03	141.57	139.44
2	137.61	140.97	128.63	138.30	133.56	128.52	140.17	139.55
3	137.23	141.78[b]	129.72	129.18	133.64	127.65	141.88[b]	139.58
4	138.23	140.81	128.77	133.63	131.97	130.17	140.03	139.24
5	138.05	139.28[c]	131.42	129.21	136.99	127.74	139.26[c]	141.86
6	138.59	139.32	130.49	132.53	135.75	129.37	140.23	139.10
7	140.18	138.90[d]	127.20	146.38	124.05	130.50	143.95	138.82[d]
8	139.97	140.21	131.98	120.96	148.53	125.69	142.43	138.86
9	138.18	149.06	-	155.82	139.49	123.31	135.65	139.01
10	137.20	139.73	125.72	138.17	153.04	-	148.46	139.16

[a] Chemical shifts of other carbon atoms [in ppm]: CH_3(3) [11.62–11.72], C3 [144.13–145.30], C9a [142.45–143.57], C11 and C15 [119.55–119.97], C12 and C14 [129.15–130.72], C13 [125.23–126.20]; [b,c,d] These signals (for each compound) can be interchanged.

Table 3. Synthetic and physical data for compounds **1–10**

	Yield[a] [%]	Mp. [°C]	Colour of crystals	Eluent[b] (TLC)	R_F	^3J(H5,H6) and/ or ^3J(H7,H8) [Hz]	^4J(H5,H7) and/ or ^4J(H6,H8) [Hz]	Absorption spectrum λ_{max} [nm]	Absorption spectrum ε_{max} [$M^{-1}cm^{-1}$]	RS[c] [%]
1	84	130-131 (131[1])	yellow	A	0.45	8.56 8.60[d]	1.35 1.30	412	3000	-
2	74	150-154	orange	B	0.42	8.78	1.91	418	3800	60
3		123-126	yellow		0.39	8.75	1.88	408	2900	40
4	78	193-196	yellow	A	0.62	9.14	2.33	418	3000	58
5		167-169	yellow		0.49	9.10	2.33	411	2200	42
6	82	184-186	yellow	A	0.64	-	-	420	3650	-
7	76	157-159	orange	A	0.47	9.40	2.55	422	3600	40
8		215-216	orange		0.34	9.34	2.37	441	2300	60
9	79	188-191 (187[1])	light brown	C	0.56	8.48[e]	1.93	413	2700	40
10		152-155	brown		0.50	3.91[f]	1.88	415	3100	60

[a] Total yield of two isomeric products; [b] A: carbon tetrachloride + *n*-hexane + ethyl acetate (6:6:1), B: light petroleum + ethyl ether (8:2), C: ethyl acetate + carbon tetrachloride (5:4); [c] Reaction selectivity (± 2 %); [d,e,f] ^3J(H6,H7) = 6.95, 4.00 and 3.91, respectively.

EXPERIMENTAL

Phenylenediamines and 2,3-diaminopyridine were commercial products (Aldrich). The literature procedure[8] was applied to prepare 3-methyl-1-phenyl-2-pyrazoline-4,5-dione. Compounds **1–10** were obtained according to Metwally's procedure.[1] All isomers separated by preparative TLC method (Kieselgel 60 F 254, Merck) were further purified by crystallization from chloroform. Melting points (determined on a Boetius apparatus) are uncorrected. Satisfactory analyses (± 0.30 % for C, H and N) were obtained for all compounds. The synthetic and physical data for compounds **1–10** are given in Table 3. UV-vis spectra were recorded on a CARY 3E spectrometer (Varian) for chloroform solutions of compounds **1–10**. Conditions for recording ^{1}H, ^{13}C NMR and 2D *z*-gradient selected $^{1}H,^{15}N$ HMBC spectra are those already described.[9] Semi-empirical AM1 calculations of the electron densities were performed using the Hyper-Chem program (version 4).

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