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SYNTHESIS OF 4-ARYL-1,3-DIPHENYL-1,4,5,10-TETRAHYDROPYRAZOLO-[3,4-*b*][1,5]BENZODIAZEPINES

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A convenient method is proposed for the synthesis of the previously unknown 4-aryl-1,3-diphenyl-1,4,5,10-tetrahydropyrazolo[3,4-b][1,5]benzodiazepines by cyclocondensation of 5-(2-aminoanilino)-1,3-diphenylpyrazole with aromatic aldehydes. The reaction only takes place very selectively with aldehydes which contain electron acceptor substituents in the aryl fragment.

Keywords: aldehydes, 1,5-benzodiazepines, pyrazoles, structure, cyclocondensation.

We have previously found that 5-(2-aminoanilino)-1,3-diphenylpyrazole (**1**) is readily formed from its more accessible trifluoroacetyl derivative of type **2** (R = CF_3) by treatment with hydrazine [1]. Acyl derivatives of general structure **2** (R = Ar, Me) and their structural analogs behave as typical N-monoacyl-substituted *o*-phenylenediamines when heated i.e. they cyclize with closing of a benzimidazole ring to give 1-pyrazolylbenzimidazoles of structure **3** [2-4]. It might be expected that cyclocondensation of compound **1** with aromatic aldehydes **4a-f** would occur similarly (involving both amino groups) to give the dihydro-substituted 1-pyrazolylbenzimidazoles **5a-f**. However, the starting pyrazole compound contains a further clear nucleophilic center, the electron rich carbon at position 4 of which could also react with an aldehyde.

We have found that reaction of compound **1** with the aldehydes **4a-f** occurs highly selectively as a cyclocondensation of a 1,6-dinucleophile with a 1,1-dielectrophile giving closure of a seven membered ring to form the previously unknown 4-aryl-1,3-diphenyl-1,4,5,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepines **6a-f** (Scheme 1).

The reaction occurs by refluxing the reagents in toluene (or ethanol in the presence of a catalytic amount of acetic aid) and is complete within 1 h. It was found to be effective when using aromatic aldehydes containing electron acceptor substituents. In the case of reaction with benzaldehyde and less reactive aromatic aldehydes a mixture of unidentified products is formed.

The composition and structure of the compounds obtained **6a-f** were confirmed by elemental analysis (Table 1) and from ^{1}H NMR spectra (Table 2).

The ^{1}H NMR spectra show that all of the synthesized compounds have a structure of one type since the fragment protons signals occurring in each of them (two phenyl and an *ortho*-phenyl ring, amino-, and a nonaromatic methine group) occur within narrow ranges of chemical shift, the changes being fully consistent with a change in the nature of the Ar substituent.

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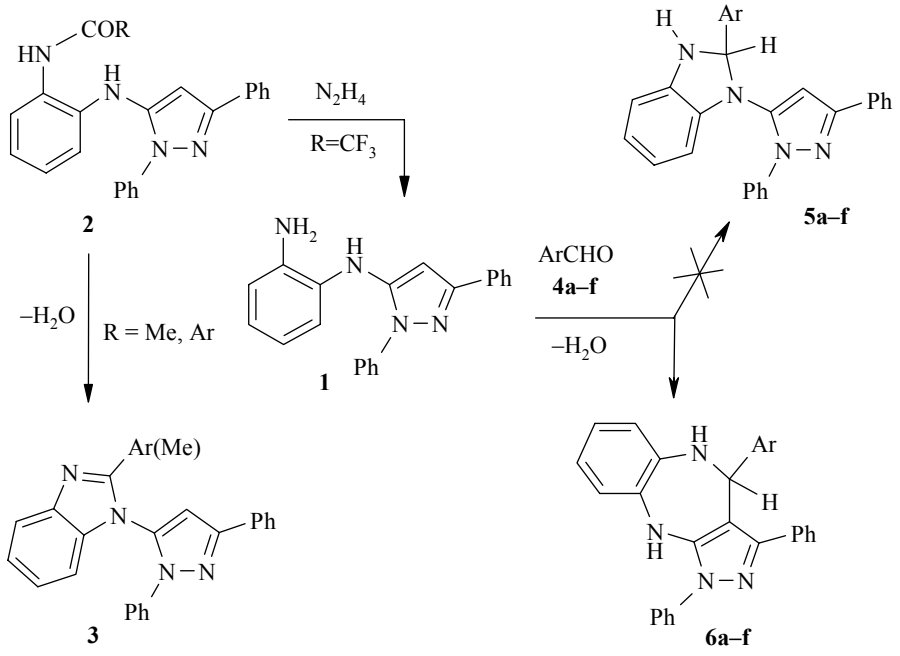
Scheme 1



4-6 a Ar = 4-$O_2NC_6H_4$, **b** Ar = 3-$O_2NC_6H_4$, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-FC_6H_4, **e** Ar = 2-pyridyl, **f** Ar = 4-pyridyl

In almost all of the compounds a particular feature is the appearance of the C-phenyl ring protons as a generally narrow multiplet in the range 7.29-7.35 ppm. In this case the reason for the absence of a differentiation of the *o*-, *m*-, and *p*-protons is the noncoplanarity of the CPh fragment relative to the pyrazole ring as a result of steric hindrance from the neighboring CHAr group. An exception from these instances is the 2-pyridyl-substituted compound **6e** in which the pyridine nitrogen atom produces a deshielding effect on the *o*-protons of the CPh group. Clearly such steric hindrance is possible only for structures **6** and is impossible in the isomeric type **5**. It is also clear that structures of type **5** contain one NH group and of type **6** two. We have studied the deuterium exchange of compound **6a** in the most often used practical conditions (20-25°C, 2 h). It was unexpectedly found that only one of the amino groups disappeared and this was the doublet, i.e. at position 5 next to the CHAr fragment. On the other hand, the proton on the nitrogen atom at position 10 resonated with a

TABLE 1. Parameters for the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
6a	$C_{28}H_{21}N_5O_2$	73.05 / 73.19	4.73 / 4.61	15.16 / 15.24	243-244.5	95
6b	$C_{28}H_{21}N_5O_2$	73.03 / 73.19	4.77 / 4.61	15.11 / 15.24	167-168.5	84
6c	$C_{28}H_{21}ClN_4$	74.82 / 74.91	4.56 / 4.71	12.37 / 12.48	228.5-231	78
6d	$C_{28}H_{21}FN_4$	77.67 / 77.76	4.83 / 4.89	12.88 / 12.95	190-191	97
6e	$C_{27}H_{21}N_5$	77.93 / 78.05	4.95 / 5.09	16.71 / 16.86	156-157.5	96
6f	$C_{27}H_{21}N_5$	77.96 / 78.05	4.92 / 5.09	16.73 / 16.86	189.5-191	72

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)
6a	5.58 (1H, d, *J* = 4.5, H-4, s, after deuterium exchange); 6.13 (1H, d, *J* = 5.7, H-5, undergoes deuterium exchange); 6.45 (1H, d, *J* = 7.8, H-6); 6.51 (1H, t, *J* = 8.1, H-7); 6.63 (1H, t, *J* = 7.8, H-8); 6.99 (1H, d, *J* = 7.8, H-9); 7.34 (5H, m, CC_6H_5); 7.47 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.53 and 8.12 (2 × 2H, two d, *J* = 8.7, 1,4-C_6H_4); 7.61 (2H, t, *J* = 7.5, NC_6H_5 H-3,5); 7.71 (2H, d, *J* = 7.8, NC_6H_5 H-2,6); 8.24 (1H, s, H-10, does not undergo deuterium exchange)
6b	(1H, d, *J* = 3.5, H-4); 6.12 (1H, d, *J* = 5.4, H-5); 6.45 (1H, d, *J* = 7.5, H-6); 6.51 (1H, t, *J* = 7.5, H-7); 6.62 (1H, t, *J* = 7.2, H-8); 6.98 (1H, d, *J* = 7.8, H-9); 7.34 (5H, m, CC_6H_5); 7.47 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.54 (1H, t, *J* = 8.4, 1,3-C_6H_4 H-5); 7.61 (2H, t, *J* = 7.5, NC_6H_5 H-3,5); 7.67-7.72 (3H, m, NC_6H_5 H-2,6 + 1,3-C_6H_4 H-6); 8.00 (1H, d, *J* = 8.7, 1,3-C_6H_4 H-4); 8.18 (1H, s, 1,3-C_6H_4 H-2); 8.25 (1H, s, H-10)
6c	5.47 (1H, d, *J* = 5.1, H-4); 5.99 (1H, d, *J* = 4.8, H-5); 6.45 (1H, d, *J* = 7.1, H-6); 6.51 (1H, t, *J* = 6.9, H-7); 6.62 (1H, t, *J* = 7.2, H-8); 6.95 (1H, d, *J* = 7.8, H-9); 7.29 (5H, m, CC_6H_5); 7.32-7.36 (4H, m, 1,4-C_6H_4); 7.46 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.60 (2H, t, *J* = 7.5, NC_6H_5 H-3,5); 7.70 (2H, d, *J* = 7.8, NC_6H_5 H-2,6); 8.17 (1H, s, H-10)
6d	5.47 (1H, d, *J* = 5.1, H-4); 5.93 (1H, d, *J* = 5.2, H-5); 6.44 (1H, d, *J* = 7.1, H-6); 6.50 (1H, t, *J* = 7.2, H-7); 6.61 (1H, t, *J* = 7.2, H-8); 6.93 (1H, d, *J* = 7.8, H-9); 7.05 and 7.36 (2 × 2H, two m, 1,4-C_6H_4); 7.31 (5H, m, CC_6H_5); 7.46 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.60 (2H, t, *J* = 7.5, NC_6H_5 H-3,5); 7.70 (2H, d, *J* = 7.8, NC_6H_5 H-2,6); 8.12 (1H, s, H-10)
6e	5.51 (1H, d, *J* = 4.8, H-4); 5.94 (1H, d, *J* = 4.5, H-5); 6.45 (1H, d, *J* = 7.5, H-6); 6.49 (1H, t, *J* = 7.5, H-7); 6.61 (1H, t, *J* = 7.2, H-8); 6.97 (1H, d, *J* = 7.8, H-9); 7.12-7.16 (2H, m, 3-C_5H_4N H-4,5); 7.31-7.32 (3H, m, CC_6H_5 H-3,4,5); 7.39 (2H, m, CC_6H_5 H-2,6); 7.45 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.60 (3H, t, *J* = 7.5, NC_6H_5 H-3,5 + C_5H_4N H-6); 7.69 (2H, d, *J* = 7.5, NC_6H_5 H-2,6); 8.15 (1H, s, H-10); 8.51 (1H, s, C_5H_4N H-3)
6f	5.46 (1H, d, *J* = 4.8, H-4); 6.08 (1H, d, *J* = 5.4, H-5); 6.47 (1H, d, *J* = 7.1, H-6); 6.52 (1H, t, *J* = 6.9, H-7); 6.63 (1H, t, *J* = 7.2, H-8); 6.96 (1H, d, *J* = 7.5, H-9); 7.23 and 8.43 (2 × 2H, two d, *J* = 5.4, 4-C_5H_4N); 7.35 (5H, m, CC_6H_5); 7.46 (1H, t, *J* = 7.2, NC_6H_5 H-4); 7.60 (2H, t, *J* = 7.2, NC_6H_5 H-3,5); 7.70 (2H, d, *J* = 8.1, NC_6H_5 H-2,6); 8.19 (1H, s, H-10)

practically unaltered integral intensity and this was due to the steric hindrance to the deuterium exchange process, probably *via* steric blocking by the neighboring N-phenyl substituent. The structure of compound **6a** was finally proved from HMQC and HMBC two dimensional heteronuclear correlation spectroscopy. The HMQC spectrum (see Fig. 1) demonstrated the linking of the hydrogen to specific carbon atoms and hence that two non equivalent hydrogen atoms bonded to nitrogen atoms are introduced into the molecular composition. Additional verification of the structure came from correlation of the proton interactions with carbon atoms via single and multiple bonds (Table 3). Analysis of the results obtained confirmed the order of the interacting atoms in the molecule as present only in structure **6a**.

According to data in [5-7] pyrazolo[3,4-*b*][1,5]benzodiazepines act upon the central nervous system. Their 1,4,5,10-tetrahydro derivatives not containing a 4-substituent are known and are prepared by reduction of the corresponding 1,10-dihydro compound [8] using sodium borohydride or the corresponding pyrazolobenzodiazepin-4-ones [9] using lithium aluminium hydride. Hence the cyclocondensation of 5-(2-aminoanilino)-1,3-diphenylpyrazole with aromatic aldehydes can be regarded as a novel and preparatively convenient synthesis of pyrazolo[3,4-*b*][1,5]benzodiazepines giving access to previously unknown compounds.

TABLE 3. ^{1}H and ^{13}C NMR Atomic Correlation Data in Compound 6a from a Cosy-Experiment

^{1}H chemical shift, δ, ppm	^{13}C chemical shifts, interacting with protons, δ, ppm	
	HMQC spectrum (interacting through one bond)	HMBC spectrum (interacting through two or three bonds)
5.58	57.68	152.71, 149.00, 143.11, 136.1, 129.36, 101.69
6.13	—*	136.12, 133.74, 123.35, 101.69
6.45	123.35	122.15
6.51	121.51	119.80, 136.12
6.63	122.15	123.35
6.99	119.80	136.12, 121.51
7.34	129.22, 127.80	133.74, 129.36, 128.12
7.47	128.12	130.20
7.53	129.36	57.68, 146.89, 129.36
7.61	130.20	130.20, 139.34
7.71	125.30	128.12, 125.30
8.12	124.12	152.71, 146.89, 124.12
8.24	—*	101.69, 119.80, 136.12

* Proton bonded to a nitrogen atom.

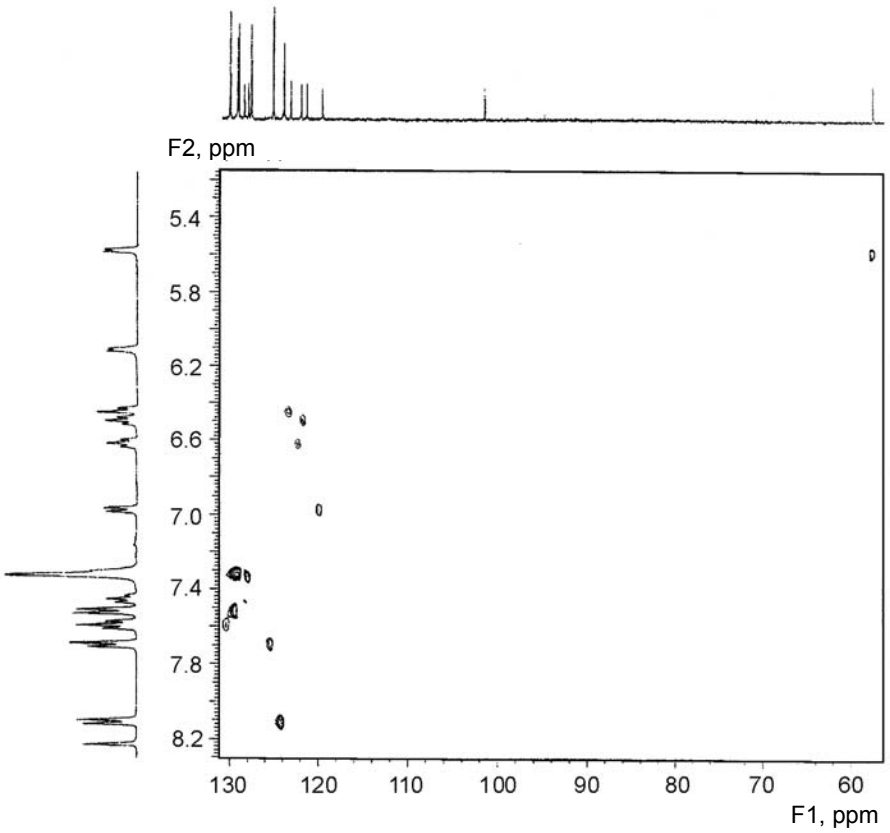


Fig. 1. C–H Correlation data (HMQC) for compound **6a**.

EXPERIMENTAL

Monitoring of the reaction course and the purity of the compounds synthesized **6a-f** was carried out by TLC on Silufol UV-254 plates in the solvent system benzene–ethanol (9:1) and revealed using UV light. Before carrying out an elemental analysis and the spectroscopic investigation the compounds **6a-d,f** were dried for 2 h at 150°C and **6e** at 115°C for 6 h in a water pump vacuum. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) using DMSO-d_6 with TMS as standard. Experiments for recording the two dimensional ^{1}H NMR and ^{13}C NMR spectra and location of the C–H correlations for compound **6a** were performed on a Varian Mercury 400 (400 MHz) spectrometer.

4-(4-Nitrophenyl)-1,3-diphenyl-1,4,5,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (6a). A mixture of compound **1** (0.326 g, 1 mmol) and aldehyde **4a** (0.136 g, 1.1 mmol) in toluene (2 ml) was refluxed with heating on an oil bath (120°C) for 1 h. After cooling, the yellow solid product was filtered off and washed with toluene. The compound was in an analytically pure state following drying. ^{13}C NMR spectrum, δ, ppm: 57.68 ($C_{(4)}$); 101.69 ($C_{(3a)}$); 119.80 ($C_{(9)}$); 121.51 ($C_{(7)}$); 122.15 ($C_{(8)}$); 123.35 ($C_{(6)}$); 124.12 (1,4-C_6H_4 $C_{(3)}$, $C_{(5)}$); 125.30 (NC_6H_5 $C_{(2)}$, $C_{(6)}$); 127.80 (CC_6H_5 $C_{(2)}$, $C_{(6)}$); 128.12 (NC_6H_5 $C_{(4)}$); 128.58 (CC_6H_5 $C_{(1)}$); 129.22 (CC_6H_5 $C_{(3)}$, $C_{(4)}$, $C_{(5)}$); 129.36 (1,4-C_6H_4 $C_{(2)}$, $C_{(6)}$); 130.20 (NPh $C_{(3)}$, $C_{(5)}$); 133.73 and 133.75 ($C_{(9a)}$ + CC_6H_5 $C_{(1)}$); 136.12 ($C_{(5a)}$); 139.34 (NC_6H_5 $C_{(1)}$); 143.11 ($C_{(10a)}$); 146.89 (1,4-C_6H_4 $C_{(4)}$), 149.00 ($C_{(3)}$); 152.71 (1,4-C_6H_4 $C_{(1)}$).

Compounds 6b,c were prepared similarly from compound **1** and the aldehydes **4b,c**.

4-(4-Fluorophenyl)-1,3-diphenyl-1,4,5,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (6d). A mixture of compound **1** (0.326 g, 1 mmol), aldehyde **4d** (0.136 g, 1.1 mmol), ethanol (2 ml), and glacial acetic acid (1 drop) was refluxed by heating on an oil bath (85°C) for 1 h. Water (1 ml) was added dropwise with stirring to the refluxing mixture. After cooling, the colorless precipitated product was filtered off and washed with a mixture of ethanol and water (1:1). After drying, the compound was obtained in an analytically pure state.

Compounds 6e,f were prepared similarly from compound **1** and aldehydes **4e,f**.

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