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AN EFFICIENT SYNTHESIS OF 1,3-DIARYL-PYRROLO[1,2-*a*]QUINOXALINES FROM 2-(1H-PYRROL-1-YL)PHENYLAMINES

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The condensation of 1,3-diaryl-4-bromo-2-buten-1-ones with o-phenylenediamine leads to 2-[2,4-diaryl-1H-pyrrol-1-yl]phenylamines. Heating solutions of these compounds in formic acid leads to formylation and intramolecular condensation to give 1,3-diarylpyrrolo[1,2-a]quinoxalines. The acylation of 2-[2,4-diphenyl-1H-pyrrol-1-yl]phenylamine with acetic anhydride in acetic acid leads to an acetamide, which readily cyclizes to give 4-methyl-1,3-diphenylpyrrolo[1,2-a]quinoxaline upon heating with $POCl_3$.

Keywords: γ-bromodypnone, 2-(1H-pyrrol-1-yl)phenylamine, N-[2-(1H-pyrrol-1-yl)phenyl]acetamide, pyrrolo[1,2-*a*]quinoxaline, polycyclic heterocyclic compounds.

The heterocyclic pyrrolo[1,2-*a*]quinoxaline system has been studied rather extensively and is the subject of more than 800 citations in the Beilstein system. Two approaches have been developed for the synthesis of such derivatives: 1) the pyrazine ring is built onto N-(2-aminophenyl)pyrrole derivatives and 2) the pyrrole ring is built onto quinoxaline derivatives. The synthesis of pyrrolo[1,2-*a*]quinoxalines using approach 1 was proposed by Cheeseman and Tuck in 1965 [1] and has been the major pathway to these compounds. However, derivatives of this tricyclic system substituted in the pyrrole segment have not been available through this approach.

In the present work, we have developed a method for the preparation of 1,3-diarylpyrrolo[1,2-*a*]quinoxalines based on our previously proposed method for the preparation of 2-(2,4-diphenyl-1H-pyrrol-1-yl)phenylamine (**1a**) [2].

In previous work [2], we described a synthesis for 2-(2,4-diphenyl-1H-pyrrol-1-yl)phenylamine (**1a**) in 61% yield by the reaction of 1,3-diphenyl-4-bromo-2-buten-1-one (γ-bromodypnone, **2a**) with *o*-phenylenediamine. The corresponding 2-[2,4-diaryl-1H-pyrrol-1-yl]phenylamines **1b** and **1c** were obtained in 60 and 66% yield, respectively, using substituted γ-bromodypnones, namely, 1,3-diaryl-4-bromo-2-buten-1-ones **2b** and **2c** [3] (see Scheme 1, Table 1). The reaction of 4-bromo-1,3-bis(4-methoxyphenyl)-2-buten-1-one **2d** with *o*-phenylenediamine leads to 2,4-bis(4-methoxyphenyl)furan [3], which does not undergo this transformation.

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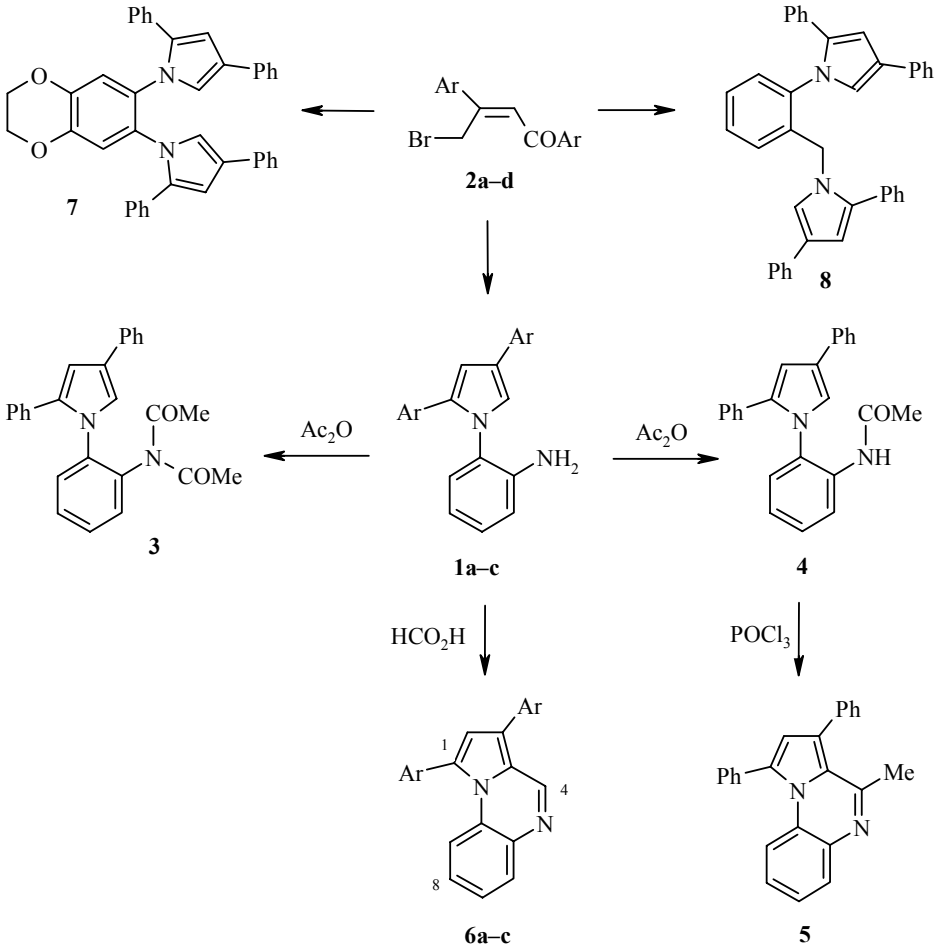

1,2,6 a Ar =Ph, **b** Ar = 4-ClC_6H_4, **c** Ar = 4-BrC_6H_4; **2d** Ar = 4-$MeOC_6H_4$

We studied the reaction of 2-[2,4-diphenyl-1H-pyrrol-1-yl]phenylamine (**1a**) with acylating agents. Heating pyrrole **1a** in acetic anhydride at reflux in the presence of sodium acetate leads to N-acetyl-N-[2-(2,4-diphenyl-1H-pyrrol-1-yl)phenyl]acetamide (**3**). This product shows no NH group signals in either the IR or ^{1}H NMR spectra. The ^{1}H NMR spectrum of acetamide **3** shows two very broadened signals for the acetyl group protons (as a consequence of steric hindrance to free rotation of the diacetylamino group) with a chemical shift difference of about 0.6 ppm. The acylation **1a** with acetic anhydride in acetic acid without heating over 1 h gave the monoacetylation product, namely, N-[2-(2,4-diphenyl-1H-pyrrol-1-yl)phenyl]-acetamide (**4**) in 51% yield. An increase in the time of maintenance of the reaction mixture leads to an increase in the yield to 70% but the product has impurities of the diacyl derivative **3**, which is difficult to remove by recrystallization.

Heating acetamide **4** in $POCl_3$ leads to intramolecular cyclization with formation of 4-methyl-1,3-diphenylpyrrolo[1,2-*a*]quinoxaline (**5**). The aromatic region in the ^{1}H NMR spectrum of quinoxaline **5** shows an upfield singlet for H-2 at 6.79 ppm and downfield doublet for H-6 at 7.90 ppm, which are clearly separated from the major group.

Attempts to carry out the cyclization of pyrroles **2a-c** to give 4-substituted pyrrolo[1,2-*a*]quinoxalines using acid chlorides proved unsuccessful. Heating of these reagents in pyridine led to a complex mixture of products including monoacylamides such as **4** in up to 30% yield as indicated by ^{1}H NMR spectroscopy.

TABLE 1. Physicochemical Properties and Elemental Analysis Data

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield %
		C	H	N	Hlg		
1b	$C_{22}H_{16}Cl_2N_2$	69.60 / 69.67	4.19 / 4.25	7.41 / 7.39	18.70 / 18.69	230-232	66
1c	$C_{22}H_{16}Br_2N_2$	56.38 / 56.44	3.42 / 3.44	6.01 / 5.98	34.14 / 34.13	248-250	60
3	$C_{26}H_{22}N_2O_2$	79.10 / 79.16	5.58 / 5.62	7.11 / 7.10	—	197-199	35
4	$C_{24}H_{20}N_2O$	81.75 / 81.79	5.64 / 5.72	7.98 / 7.95	—	93-94	51
5	$C_{24}H_{18}N_2$	86.15 / 86.20	5.40 / 5.43	8.40 / 8.38	—	141-143	41
6a	$C_{23}H_{16}N_2$	86.17 / 86.22	4.97 / 5.03	8.74 / 8.74	—	162-164	68
6d	$C_{23}H_{14}Cl_2N_2$	70.90 / 70.96	3.58 / 3.62	7.22 / 7.20	18.20 / 18.21	201-203	70
6c	$C_{23}H_{14}Br_2N_2$	57.72 / 57.77	2.89 / 2.95	5.85 / 5.86	33.44 / 33.42	203-205	65
7	$C_{40}H_{30}N_2O_2$	84.12 / 84.19	5.25 / 5.30	4.93 / 4.91	—	258-260	27
8	$C_{39}H_{30}N_2$	88.88 / 88.94	5.69 / 5.74	5.31 / 5.32	—	94-96	43

*Solvent: $MeNO_2$ for **1b**, DMF for **1c, 6c,d, 7**, 2-propanol for **3-5**, hexane for **6a**, and ethanol for **8**.

The reaction of pyrrolylphenylamines **1a-c** with formic acid leads directly to cyclic products, namely, 1,3-diarylpyrrolo[1,2-*a*]quinoxalines **6a-c**. The only difference from the procedure for the preparation of unsubstituted quinoxalines proposed by Cheeseman [4] is the heating time. A total of 8 h heating at reflux was required for the complete conversion of amines **1a-c** to quinoxalines **6a-c**. The ^{1}H NMR spectra of quinoxalines **6a-c** show a singlet for H-4 at 8.97 ppm, which is characteristic for pyrrolo[1,2-*a*]quinoxalines unsubstituted at C-4.

Comparison of our results on the cyclization of **1** to give **6** with the cyclization of 2-(pyrrol-1-yl)phenylamine [4] indicates a lower reactivity for phenylamines **1** due to the introduction of two aryl substituents into the pyrrole ring. Variation of the substituents in the aryl rings has no significant effect on the cyclization of **1** to **6**.

We should note that 1,3-diarylpyrrolo[1,2-*a*]quinoxalines **5** and **6a-c** lack basic properties and do not form salts with mineral acids or quaternary salts with methyl iodide and benzyl chloride (in nitromethane).

We then attempted to expand the variety of 1,3-diarylpyrrolo[1,2-*a*]quinoxalines available by means of the methods described above through variation of the structure of the *o*-phenylenediamines used in the first step. However, the major product of the reaction of γ-bromodypnone **2a** with *o*-phenylenediamines which have electron-withdrawing groups (4–Cl, 4-NO_2), was 2,4-diphenylfuran, which was found as the product of heating γ-bromodypnone **2a** in the presence of base [3, 8]. On the other hand, complex mixtures containing the expected pyrroles and bispyrroles were obtained using *o*-phenylenediamines, which have electron-donor groups (4-Me, 4-OMe). 1-[7-(2,4-Diphenylpyrrol-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,4-diphenyl pyrrole (**7**) was isolated and characterized only in the case of 6,7-diamino-2,3-dihydro-1,4-benzodioxin. The structure of pyrrole **7** was established by mass spectrometry as well as IR and ^{1}H NMR spectroscopy. These spectra showed the lack of NH group signals. The reaction of γ-bromodypnone **2a** with 2-(aminomethyl)aniline leads to a similar result and the isolation of 1-{2-[(2,4-diphenylpyrrol-1-yl)-methyl]phenyl}-2,4-diphenylpyrrole (**8**). An interesting feature in the ^{1}H NMR spectrum of pyrrole **8** is the finding of signals for the magnetically-nonequivalent methylene group protons as an AB spin system with J = 16.8 Hz as a consequence of steric hindrance to rotation about the C–N single bonds.

EXPERIMENTAL

The IR spectra were taken for CsI pellets on a Pye-Unicam SP3-300 spectrometer. The ^{1}H NMR spectra were taken on a Varian Mercury 400 spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The chemical ionization mass spectra were taken with separation by HPLC on an Agilent 1200 SL system (CI, acetonitrile and 0.05% formic acid). The reaction course and purity of the products were monitored using thin-layer chromatography on Silufol UV-254 plates.

Samples of 1,3-diaryl-4-bromo-2-buten-1-ones **2b** and **2c** were obtained according to our previous procedure [3].

2-[2,4-Bis(4-chlorophenyl)pyrrol-1-yl]phenylamine (1b) and 2-(2,4-Bis(4-bromophenyl)pyrrol-1-yl]phenylamine (1c) were obtained according to the procedure described for phenylamine **1a** in our previous work [2].

Phenylamine 1b. IR spectrum, ν, cm^{-1}: 3461 (NH_2), 3374 (NH_2), 1617, 1501, 1484, 1089, 832, 797, 749. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.58 (2H, d, ^3J = 8.5, H-2', H-6'); 7.31 (2H, d, ^3J = 8.5, H-3', H-5'); 7.26 (1H, d, ^3J = 1.6, H-α); 7.18-7.16 (4H, m, H-2", H-3", H-5", H-6"); 7.09 (1H, t, ^3J = 8.0, H-4); 6.90 (1H, d, ^3J = 8.0, H-6); 6.83 (1H, d, ^3J = 1.6, H-β); 6.80 (1H, d, ^3J = 8.0, H-3); 6.55 (1H, t, ^3J = 8.0, H-5); 4.72 (2H, s, NH_2).

Phenylamine 1c. IR spectrum, ν, cm^{-1}: 3461 (NH_2), 3373 (NH_2), 1617, 1503, 1480, 1008, 829, 796, 759. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52 (2H, d, ^3J = 8.5, H-2', H-6'); 7.44 (2H, d, ^3J = 8.5, H-3', H-5'); 7.32 (2H, d, ^3J = 8.5, H-2", H-6"); 7.25 (1H, d, ^3J = 1.6, H-α); 7.12 (2H, d, ^3J = 8.5, H-3", H-5"); 7.09 (1H, t, ^3J = 8.0, H-4); 6.90 (1H, d, ^3J = 8.0, H-6); 6.83 (1H, d, ^3J = 1.6, H-β); 6.80 (1H, d, ^3J = 8.0, H-3); 6.55 (1H, t, ^3J = 8.0, H-5); 4.70 (2H, s, NH_2).

N-Acetyl-N-[2-(2,4-diphenylpyrrol-1-yl)phenyl]acetamide (3). Sodium acetate (0.2 g) was added to a solution of phenylamine **1a** (0.31 g, 1.0 mmol) in acetic anhydride (5 ml). The mixture was heated at reflux for 3 h. The excess acetic anhydride was evaporated in vacuum and 10 ml water was added to the residue. The solid was filtered off and washed with water and 2-propanol. IR spectrum, ν, cm^{-1}: 1691 (C=O), 1601, 1518, 1475, 1298, 757, 691. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.61 (1H, d, ^3J = 7.5, H-6); 7.54 (1H, t, ^3J = 7.5, H-4); 7.50-7.48 (3H, m, H-2', H-6', H-5); 7.39 (1H, d, ^3J = 7.5, H-3); 7.31 (2H, t, ^3J = 8.0, H-3', H-5'); 7.22-7.12 (6H, m, H-2", H-3", H-4", H-5", H-6", H-4'); 6.93 (1H, d, ^3J = 1.4, H-α); 6.66 (1H, d, ^3J = 1.4, H-β); 2.07 (3H, br. s, CH_3); 1.40 (3H, br. s, CH_3).

N-[2-(2,4-diphenylpyrrol-1-yl)phenyl]acetamide (4). Acetic anhydride (0.5 ml, 5.3 mmol) was added to a solution of phenylamine **1a** (0.31 g, 1.0 mmol) in acetic acid (5 ml). The mixture was stirred at room temperature for 1 h. Then, water (25 ml) was added with ice cooling. After 30 min, the precipitate formed was filtered off. IR spectrum, ν, cm^{-1}: 3420 (NH), 1680 (C=O), 1600, 1518, 1480, 1455, 1298, 755, 692. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.04 (1H, br. s, NH); 7.58 (2H, d, ^3J = 7.5, H-2', H-6'); 7.33-7.31 (5H, m, H-3', H-5', H-4, H-5, H-6); 7.26 (1H, d, ^3J = 1.4, H-α); 7.17-7.06 (6H, m, H-2', H-3", H-4", H-5", H-6", H-4'); 7.00 (1H, m, H-3); 6.76 (1H, d, ^3J = 1.4, H-β); 1.89 (3H, br. s, CH_3).

4-Methyl-1,3-diphenylpyrrolo[1,2-*a*]quinoxaline (5). A solution of acetamide **4** (0.4 g, 1.13 mmol) in phosphoryl chloride (7 ml) was heated at reflux for 30 min. The solvent was evaporated off and 30 ml ice water was added to the residue. The precipitate of 4-methyl-1,3-diphenylpyrrolo[1,2-*a*]quinoxaline hydrochloride was filtered off. The solid was dissolved in 10 ml warm water and 2 ml 10% aq. Na_2CO_3 was added. After 1 h, the precipitate formed was filtered off and thoroughly washed with water and 2-propanol. IR spectrum, ν, cm^{-1}: 1600 (C=N), 1475, 1410, 1330, 765, 705. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (1H, d, ^3J = 8.0, H-6); 7.56-7.55 (5H, m, H Ar); 7.43-7.30 (7H, m, H Ar); 7.14 (1H, t, ^3J = 8.0, H-7); 6.79 (1H, s, H-2); 2.39 (3H, s, CH_3).

1,3-Diphenylpyrrolo[1,2-*a*]quinoxaline (6a). Phenylamine **1a** (0.5 g, 1.61 mmol) was dissolved in formic acid (5 ml) with heating. The mixture was heated at reflux for 8 h. The excess acid was evaporated off

and 10 ml 10% aq. Na_2CO_3 was added. The solid was filtered off and thoroughly washed with water and a small amount of 2-propanol. IR spectrum, ν, cm^{-1}: 3065, 1600 (C=N), 1450, 1323, 755, 745, 693. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.97 (1H, s, H-4); 7.84 (1H, d, ^3J = 8.0, H-6); 7.66 (2H, d, ^3J = 8.0, H-2', H-6'); 7.56-7.54 (5H, m, H-3', H-4', H-5', H-2", H-6"); 7.49 (2H, t, ^3J = 8.0, H-3", H-5"); 7.36-7.35 (3H, m, H-8, H-9, H-4"); 7.15 (1H, t, ^3J = 8.0, H-7); 6.98 (1H, s, H-2). Chemical ionization mass spectrum, *m/z* (I_{rel}, %): 321 $[M+1]^+$ (100), 322 $[M+2]^+$ (43).

1,3-Bis(4-chlorophenyl)pyrrolo[1,2-*a*]quinoxaline (6b) and 1,3-Bis(4-bromophenyl)pyrrolo-[1,2-*a*]quinoxaline (6c) were obtained according to the procedure for quinoxaline **6a** using 10 ml formic acid.

Quinoxaline 6b. IR spectrum, ν, cm^{-1}: 3045, 1612 (C=N), 1491, 1470, 1425, 1324, 1090, 819, 766. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.97 (1H, s, H-4); 7.86 (1H, d, ^3J = 8.0, H-6); 7.67 (2H, d, ^3J = 8.0, H-2', H-6'); 7.57-7.56 (4H, m, H-3', H-5', H-2", H-6"); 7.48 (2H, t, ^3J = 8.0, H-3", H-5"); 7.39-7.38 (2H, m, H-8, H-9); 7.22 (1H, t, ^3J = 8.0, H-7); 7.00 (1H, s, H-2).

Quinoxaline 6c. IR spectrum, ν, cm^{-1}: 3050, 1611 (C=N), 1470, 1422, 1324, 1075, 1006, 818, 765. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.96 (1H, s, H-4); 7.85 (1H, d, ^3J = 8.0, H-6); 7.69 (2H, d, ^3J = 8.0, H-2', H-6'); 7.61 (4H, m, H-3', H-5', H-2", H-6"); 7.50 (2H, t, ^3J = 8.0, H-3", H-5"); 7.39 (2H, m, H-8, H-9); 7.22 (1H, t, ^3J = 8.0, H-7); 7.00 (1H, s, H-2).

1-[7-(2,4-Diphenylpyrrol-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,4-diphenylpyrrole (7). A mixture of γ-bromodypnone **2a** (1.0 g, 3.32 mmol), sodium acetate (0.27 g), and (0.55 g, 3.32 mmol) 7-amino-2,3-dihydro-1,4-benzodioxin-6-ylamine was fused on an oil bath at 120-130°C for 5 min. After cooling, 10 ml water was added to the melt and thoroughly triturated. The solid residue was filtered off, thoroughly washed with water and 2-propanol, and recrystallized. IR spectrum, ν, cm^{-1}: 1600, 1500, 1298, 1205 (C-O), 1065, 770, 700. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.27-7.23 (9H, m, H Ar, 2H-α); 7.10-6.92 (11H, m, H Ar); 6.73-6.71 (4H, m, H-5, H-8, 2H-4"); 6.38 (2H, br. s, 2H-β); 4.36-4.35 (4H, m, $O(CH_2)_2O$. Chemical ionization mass spectrum, *m/z* (I_{rel}, %): 571 $[M+1]^+$ (100), 572 $[M+2]^+$ (50).

1-{2-[(2,4-Diphenylpyrrol-1-yl)methyl]phenyl}-2,4-diphenylpyrrole (8) was obtained according to the procedure described above for pyrrole **7** using 2-(aminomethyl)aniline (0.4 g, 3.32 mmol). IR spectrum, ν, cm^{-1}: 3027, 2937, 1600, 1490, 1395, 1230, 760, 690. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.58 (2H, d, ^3J = 8.5, H-2', H-6'); 7.40 (2H, d, ^3J = 8.0, H-2"', H-6"'); 7.35-7.33 (5H, m, H-3', H-4', H-5', H-2", H-6"); 7.26-7.24 (5H, m, H-3"', H-4"', H-5"', H-2"", H-6""); 7.17-7.15 (6H, m, H-3", H-4", H-5", H-3"', H-4"', H-5"'); 7.08 (1H, t, ^3J = 8.0, H-4); 6.99-6.97 (3H, m, H-5, H-6, H-α); 6.78 (1H, d, ^3J = 1.6, H-β); 6.45 (1H, d, ^3J = 1.6, H-β'); 4.94 (1H, d, ^2J = 16.8, $C\underline{H}_AH_B$); 4.73 (1H, d, ^2J = 16.8, $CH_AC\underline{H}_B$).

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