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Dibenzoxepino[4,5-*d*]pyrazoles: a facile approach via the Ullmann-ether reaction

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Abstract

The application of a synthetic sequence of amine-exchange/Ullmann-ether reaction to 1,2-diarylenaminoketones for the access to dibenzoxepino[4,5-*d*]pyrazoles is reported. The reaction proceeds efficiently, permitting to incorporate a variety of substituents.

Keywords: dibenzoxepines; Ullmann reaction; exchange reaction.

It is well known that the preparation of new tetracyclic compounds bearing the azepine or oxepine ring led to a new era in the field of pharmacopsychiatry.[1] In this context, the antipsychotic properties exhibited by dibenzoxepino[*b*,*f*]fused heterocycles such as maroxepine, savoxepine[2a] and the pyrrolidine ORG-5222,[2b] provide an alternative to the employment of azepine derivatives in the treatment of anxiety disorders and psychosis of schizophrenic origin. Compounds with the formerly mentioned framework have found applications to a lesser extent against certain types of ovary cancer,[3a] as antiinflammatory[3b] or as antispasmodic agents.[3c] Encouraged by these antecedents, we embarked on a project directed at the synthesis of the title derivatives with the aim of exploring their biological properties.[4] In this paper, we wish to report an efficient and facile method for the synthesis of tetracycles **1**. Our synthetic strategy was designed as shown in Scheme 1. This challenging approach relies on the successful cyclization of the halohydroxyaryl pyrazoles **2** into the fused system **1**, contrasting with the literature procedures for the syntheses of dibenzoxepines, generally based on preformed diaryl ether derivatives.[5] Following our ongoing research on the chemistry of new phenanthro heterocyclic compounds,[6] we planned to prepare the required diarylpyrazoles **2** by amine-exchange reaction of the corresponding 1,2-diarylenaminoketones **3**.

The synthetic pathway carried out is outlined in Scheme 1. Thus, enaminoketones **3**,[7] easily obtained by aminomethylenation of the corresponding aryl benzyl ketones[8] with dimethylformamide dimethyl acetal, were transformed into the 1-phenyl-4,5-diarylpyrazoles **2** by amine-exchange/heterocyclization with phenylhydrazine, leading regioselectively to the target heterocycle

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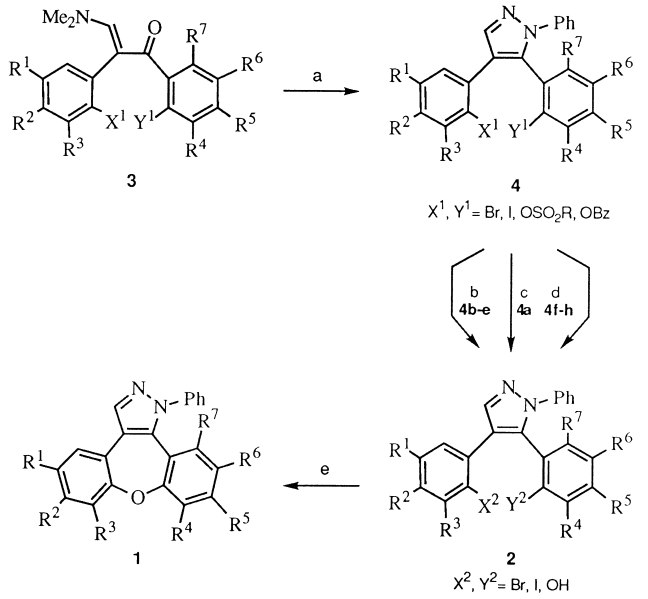

Scheme 1. Reagents and conditions. (a) $PhNH–NH_2·HCl$, $MeOH–H_2O$, Na_2CO_3/AcOH (pH = 4), 140°C, 9–15 h; (b) KO^{t}Bu, DMF, 0°C, 0.25 h, (c) NaOH, $MeOH–H_2O$, $NBnEt_3Cl$ (8 mol%) (sealed tube), 9 h; (d) KOH, $MeOH–H_2O$, 70°C, 2 h; (e) $CuBr·SMe_2$, NaH, Py, 120°C, 2–8 h

4. This approach overwhelms the lack of regioselectivity classically associated with the usual reaction between 1,3-dicarbonyl compounds and hydrazines.[9] The deprotection step, performed by basic hydrolysis, furnished the halohydroxy pyrazoles **2** in excellent yields, except in the case of the tosylate **2a**, which required unexpectedly harsh hydrolysis conditions.

Finally, after screening a variety of copper derivatives such as Cu_2O, CuI, CuCl, CuO, CuOTf and Cu in DMSO, DMF, NMP or toluene, the crucial Ullmann-ether reaction was successfully effected by treating the sodium phenoxides in situ generated from pyrazoles **4**, with the complex $CuBr·SMe_2$ in pyridine, leading to the formation of the target dibenzoxepines **1** in good yield (Table 1).[10,11] We found that in the presence of copper(I) 2-thiophenecarboxylate (CuTC), the reaction took place with comparable efficiency.[12]

Table 1
Synthesis of dibenzoxepinopirazoles **1** and pyrazoles **2** and **4**

X^1	Y^1	X^2	Y^2	R^1	R^2	R^3	R^4	R^5	R^6	R^7	**4** (%)[a]	**2** (%)[a]	**1** (%)[a]
I	OTs	I	OH	H	H	H	H	H	H	H	**4a** (90)	**2a** (88)	**1a** (87)
I	OSO_2Ph	I	OH	H	H	H	H	NEt_2	H	H	**4b** (91)	**2b** (64)[b]	**1b** (57)[b]
OSO_2Ph	I	OH	I	H	H	H	H	OMe	OMe	H	**4c** (94)	**2c** (79)	**1c** (69)
OSO_2Ph	I	OH	I	Cl	H	H	H	H	H	H	**4d** (63)	**2d** (69)	**1d** (88)
OSO_2Ph	I	OH	I	Cl	H	Cl	H	H	H	H	**4e** (12)	**2e** (82)	**1e** (76)
I	OBz	I	OH	OMe	OMe	H	H	OMe	H	OMe	**4f** (85)	**2f** (98)	**1f** (72)
I	OBz	I	OH	OMe	OMe	H	OMe	OMe	H	H	**4g** (92)	**2g** (95)	**1g** (74)
Br	OBz	Br	OH	OMe	OMe	H	OMe	OMe	H	H	**4h** (91)	**2h** (81)	**1g** (78)

[a] Isolated yield of crystallized product unless otherwise noted.

[b] Isolated yield by column chromatography.

It is noteworthy that the reaction yield is not dependent on the electronic nature of the substituents. However, in terms of the phenol component of the reaction, the substrates bearing electron-withdrawing groups **2d–e** were found to react considerably faster, compared to the electron-rich (**2b–c** and **2f–h**) or -neutral phenols (**2a**).

In summary, our synthetic pathway provides an efficient access to dibenzoxepino[4,5-*d*]pyrazoles by using a modern variant of the Ullmann reaction, that operates in relatively mild conditions and allows the accommodation of a variety of substitution patterns. Besides, it provides a practical alternative to other known methodologies for the synthesis of dibenzoxepine derivatives. Application of our synthetic pathway to the construction of thiepine derivatives and other dibenzoxepino-fused heterocycles is currently under way.

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10. Typical procedure for the Ullmann-ether coupling of halohydroxypyrazoles **2**: NaH was added in portions (95%, 24 mg, 0.9 mmol) to a stirred solution of the pyrazole **2c** (441 mg, 0.88 mmol) and $CuBr{\cdot}SMe_2$ (355.5 mg, 1.74 mmol) in dry pyridine (9.5 mL) under Ar. After stirring the resulting mixture at room temperature for 15 min, it was heated at 120°C for 4.5 h and then cooled to room temperature. The reaction was quenched with HCl (5%) (80 ml), stirred at room temperature for 30 min and extracted with CH_2Cl_2. The organic layer was washed with a solution of $CuSO_4$, dried over anhydrous Na_2SO_4 and the solvent was eliminated in vacuo. The obtained viscous residue was purified by flash column chromatography (SiO_2, 80% CH_2Cl_2/hexane) and the resulting oil was crystallized from Et_2O affording the dibenzoxepine **1c** as a white powder (225 mg, 69%).
11. All new compounds showed analytical and spectroscopic data consistent with the reported structure. Selected data for representative compounds: (a) 10,11-Dimethoxy-1-phenyldibenzo[2,3:6,7]oxepino[4,5-d]pyrazole **1c** (m.p.:

166–167°C (Et_2O)): 250 MHz ^1H NMR ($CDCl_3$) δ 3.30 (3H, s, OMe), 3.90 (3H, s, OMe), 6,20 (1H, s, H_{arom}), 6,90 (1H, s, H_{arom}), 7.20–7.27 (1H, m, H_{arom}), 7.30 (1H, dd, $J = 8.1$, 1.5 Hz, H_{arom}), 7.38–7.58 (7H, m, H_{arom}) and 8.03 (1H, s, H-3); 63 MHz ^{13}C NMR ($CDCl_3$) δ 55.4, 56.0 (OMe), 105.5, 110.1 (C_{arom}-H), 113.9, 119.6 (C_{arom}-C, C-4), 121.3, 125.5 (C_{arom}-H), 125.7 (C_{arom}-C), 127.1, 128.0, 128.5, 129.2 (C_{arom}-H), 136.4 (C_{arom}-N), 137.8 (C-3), 140.0 (C-12b) and 145.6, 150.4, 155.9 (C_{arom}-O); EIMS (*m*/*z*,%) 370 (M^+, 100), 323 (15), 295 (24), 169 (13), 77 (17). Anal. calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.49; H, 4.96; N, 7.61. (b) 5-(4,5-Dimethoxy-2-iodophenyl)-4-(2-hydroxyphenyl)-1-phenylpyrazole **2c** (m.p.: 225–226°C (EtOAc)): 250 MHz ^1H NMR ($CDCl_3$) δ 3.66 (3H, s, OMe), 3.83 (3H, s, OMe), 5.52 (1H, bs, OH), 6.68 (1H, s, H_{arom}), 6.78 (1H, ddd, $J = 8.5$, 7.6, 1.2 Hz, H_{arom}), 6.88 (1H, dd, $J = 8.3$, 1.2 Hz, H_{arom}), 6.97 (1H, dd, $J = 7.7$, 1.9 Hz, H_{arom}), 7.13 (1H, s, H_{arom}), 7.17 (1H, ddd, $J = 8.5$, 8.3, 1.9 Hz, H_{arom}), 7.28–7.32 (5H, m, H_{arom}), and 7.93 (1H, s, H–3); 63 MHz ^{13}C NMR ($CDCl_3$) δ 56.0 (OMe), 89.0 (C_{arom}-I), 114.3, 115.5 (C_{arom}-H), 117.6, 118.6 (C_{arom}-C, C-4), 120.3, 121.2, 124.2 (C_{arom}-H), 125.3 (C_{arom}-C), 127.2, 128.2, 128.9, 130.7 (C_{arom}-H), 139.8 (C_{arom}-N), 140.3 (C-3), 142.4 (C-5), 149.1, 149.7 (C_{arom}-O) and 153.4 (C_{arom}-OH); EIMS (*m*/*z*,%) 498 (M^+, 39), 371 (100), 355 (25), 327 (10), 77 (35). Anal. Calcd for $C_{23}H_{19}IN_2O_3$: C, 55.44; H, 3.84; N, 5.62. Found: C, 55.39; H, 3.80; N, 5.69.

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