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LETTERS

2-Alkyl-1-(2-aryl-1,1-difluoro-2-hydroxyethyl)benzimidazoles: potential angiotensin II receptor antagonists

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Abstract

2-Alkyl-1-(bromodifluoromethyl)benzimidazoles were synthesized and condensed with aromatic aldehydes to give 2-alkyl-1-(2-aryl-1,1-difluoro-2-hydroxyethyl)-benzimidazoles. A potential nonpeptide antagonist of the angiotensin II receptor with the -$CF_2CH(OH)$-bridge between the heterocyclic nitrogen atom and the biphenyl moiety was synthesized.

Numerous derivatives of imidazole and benzimidazole with a biphenyl group attached to the nitrogen atom of the heterocyclic ring through a methylene bridge have been described. Some of these compounds exhibit the ability to block receptors of angiotensin II and to prevent thereby its hypertensive effect.[1,2] The introduction of lipophilic difluoromethylene and reactive -CH(OH)-groups instead of the methylene bridge offers considerable scope for the synthesis of new biologically active compounds.

The condensation of 2-bromodifluoromethylbenzoxazole and 5-bromodifluoromethyl-3-phenyloxadiazole with aldehydes and tetrakis(dimethylamino) ethylene (TDAE) as the reducing agent was reported recently.[3] Similar reactions of compounds with a bromodifluoromethyl group at the nitrogen rather than at the carbon atom have not yet been studied. Moreover, benzimidazoles with the CF_2Br group on the nitrogen atom are unknown.

In this letter we describe the synthesis of 2-alkyl-1-bromodifluoromethylbenzimidazoles and their condensation with aromatic aldehydes.

2-Alkyl-1-bromodifluoromethylbenzimidazoles were obtained by treating sodium salts of 2-alkylbenzimidazoles with dibromodifluoromethane in dry acetonitrile in the presence of Zn powder as the catalyst[4](Scheme 1).

The bromodifluoromethylated derivatives obtained in this way react with aromatic aldehydes in the presence of TDAE[5] (Scheme 2).

The condensation of the *N*-bromodifluoromethyl-2-alkylbenzimidazoles proceeds under more severe conditions than in the case of 2-bromodifluoromethylbenzoxazole.

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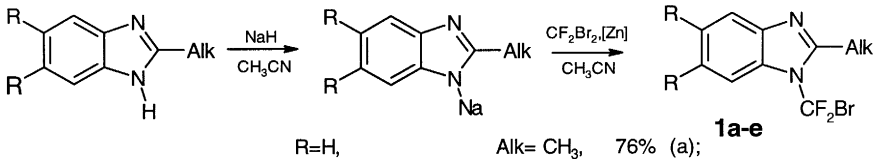
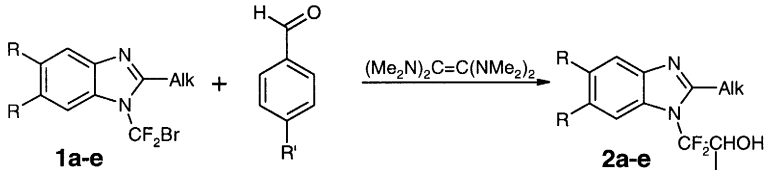


R=H, Alk= CH_3, 76% (a);
R=H, Alk= C_3H_7, 80% (b);
R=H, Alk= CH_2Ph, 72% (c);
R=Cl, Alk= CH_3, 70% (d);
R= -CH=CH-CH=CH-, Alk=CH_3, 81% (e)

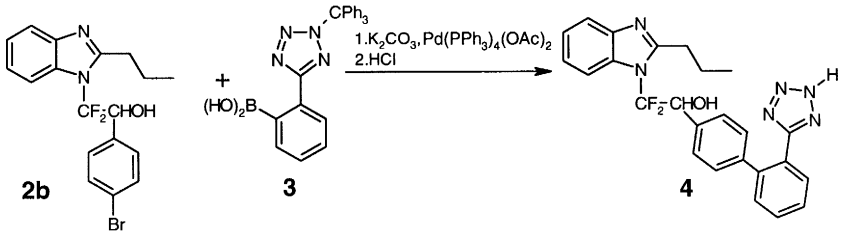
Scheme 1.



R= H, Alk= CH_3, R'= H, 46% (a);
R= H, Alk= C_3H_7, R'= Br, 55% (b);
R= H, Alk= CH_2Ph, R'= OCH_3, 34% (c);
R= Cl, Alk= CH_3, R'= F, 46% (d);
R=-CH=CH-CH=CH-, Alk=CH_3, R'= Br, 27% (e)

Scheme 2.

Compound (**2b**) was cross-coupled with arylboronic acid (**3**) by the reported procedure[6] to afford (**4**),[7] a potential antagonist of the angiotensin II receptor (Scheme 3).



Scheme 3.

The difluoromethylene group is not hydrolyzed on removal of the triphenylmethyl protection.

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2. Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*, 877.
3. Burkholder, C.; Dolbier Jr.,W. R.; Medebielle, M. *J. Org. Chem.* **1998**, *63*, 5385.
4. Typical procedure for the synthesis 2-alkyl-1-bromodifluoromethybenzimidazoles (**1a**–**e**). To a stirred solution of 2-alkylbenzimidazole (20 mmol) in 50 ml of anhydrous acetonitrile, under an argon atmosphere at −15°C, was added zinc powder (0.1 g, 1.5 mmol) and then, sodium hydride (0.53 g, 22 mmol) in portions. The mixture was stirred at −10 to −5°C for 3 h, cooled to −15°C and dibromodifluoromethane (2.74 ml, 30 mmol) was added dropwise. The reaction mixture was warmed to 20°C in 2 h and stirred at this temperature for a further 14 h. The solvent was evaporated under reduced pressure and the residue was extracted with hot hexane (3×50 ml). The extract was filtered and evaporated to leave a brown oil, which was purified by vacuum distillation or by crystallization (hexane). Compound **1a**: mp 29–30°C, bp 80–82°C (0.01 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.77 (s, 3H), 7.3–7.9 (m, 4H); ^{19}F NMR (288 MHz, $CDCl_3$, $CFCl_3$): δ −27.76 (s,

CF_2Br). Compound **1b**: mp 44–45°C, bp 102–103°C (0.01 mmHg), ^1H NMR (CD_3COCD_3, TMS): δ 0.98 (t, 3H), 1.79 (spt, 2H), 2.28 (t, 2H), 7.22–7.9 (m, 4H); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −27.51 (s, CF_2Br). Compound **1c**: mp 44–45°C, ^1H NMR ($CDCl_3$, TMS): δ 4.35 (s, 2H), 7.1–7.9 (m, 9H); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −27.24 (s, CF_2Br). Compound **1d**: mp 76–78°C, ^1H NMR ($CDCl_3$, TMS): δ 2.66 (s, 3H), 7.61 (s, 1H), 7.71 (s, 1H); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −28.04 (s, CF_2Br). Compound **1e**: mp 93–95°C, ^1H NMR ($CDCl_3$, TMS): δ 2.80 (s, 3H), 7.4–8.2 (m, 6H); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −26.81 (s, CF_2Br).

5. Typical procedure for synthesis of 2-alkyl-1-(2-aryl-1,1-difluoro-2-hydroxyethyl)-benzimidazoles (**2a**–**e**). In a three-necked flask equipped with a drying tube, thermometer, and an argon inlet tube were placed, under argon at −10°C a solution of 2-alkyl-1-bromodifluoromethylbenzimidazole (**1a**–**e**) (10 mmol) in 15 ml of dry DMF and the aromatic aldehyde (30 mmol). After stirring at −10°C for 20 min, TDAE (5.1 ml, 22 mmol) was added dropwise and the stirring was continued for 1 h, after which time the mixture was warmed to room temperature over 1 h, stirred for 28 h, heated to 40°C and stirred at this temperature for a further 5 h. The solvent was evaporated under reduced pressure, the residue was dried in vacuum (0.01 mmHg, 40–45°C) for 3 h, cooled to room temperature, diluted with water (50 ml) and diethyl ether (30 ml) and stirred for 5 h. The organic layer was separated, the aqueous solution was extracted with ether (3×30 ml), and the combined extracts were washed with saturated aqueous NaCl solution (2×50 ml), dried ($MgSO_4$), and filtered. Evaporation of the solvent gave a crude product, which was purified by crystallization (benzene:hexane 1:1). Compound **2a**: mp 172–173°C, ^1H NMR (CD_3COCD_3, TMS): δ 2.76 (s, 3H), 5.63 (dd, 1H), 7.01 (br.s, OH), 7.2–7.8 (m, 9H); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −86.34 (d, $J_{F–F}$=219 Hz), −90,66 (d, $J_{F–F}$=219 Hz). Compound **2b**: mp 186–187°C, ^1H NMR (CD_3COCD_3, TMS): δ 0.93 (t, 3H), 1.77 (spt, 2H), 2.64 (t, 2H), 5.34 (dd, 1H), 6.94 (br.s, OH), 7.2–7.8 (m, 8H); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −83.73 (d, $J_{F–F}$=217 Hz), −89.67 (d, $J_{F–F}$=217 Hz). Compound **2c**: mp 166–167°C, ^1H NMR (CD_3COCD_3, TMS): δ 4.02 (s, 3H), 4.31 (s, 2H), 5.34 (dd, 1H), 6.94 (br.s, OH), 7.2–7.8 (m, 13H); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −84.43 (d, $J_{F–F}$=218 Hz), −89.66 (d, $J_{F–F}$=218 Hz). Compound **2d**: mp 235–237°C, ^1H NMR (CD_3COCD_3, TMS): δ 2.46 (s, 3H), 5.63 (dd, 1H), 6.19 (br.s, OH), 7.1–7.8 (m, 6H); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −85.36 (d, $J_{F–F}$=222 Hz), −90.38 (d, $J_{F–F}$=222 Hz), −113.01 (s, 1F). Compound **2e**: mp 229–232°C, ^1H NMR ($CDCl_3$, TMS): δ 2.54 (s, 3H), 5.38 (dd, 1H), 6.34 (br.s, OH), 7.0–7.8 (m, 10H); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −86.35 (d, $J_{F–F}$=231 Hz), −96.03 (d, $J_{F–F}$=231 Hz).

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7. Data for compound **4**: mp 149–151°C, ^1H NMR (CD_3COCD_3, TMS): δ 0.99 (t, 3H), 1.87 (spt, 2H), 2.77 (t, 2H), 5.59 (dd, 1H), 6.21 (br.s, OH), 7.2–7.9 (m, 12H), 8.19 (s, NH); ^{19}F NMR (CD_3COCD_3, $CFCl_3$): δ −84.72 (d, $J_{F–F}$=218 Hz), −89.97 (d, $J_{F–F}$=218 Hz).