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One-pot synthesis of new heterocycles: 2,4-disubstituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines

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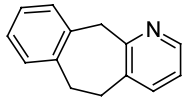
Abstract—The reaction of 1-benzosuberone with nitriles in the presence of triflic anhydride affords in good yields 2,4-diaryl substituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines, a new class of heterocycle.

Compounds with the benzocyclohepta bicycle fused to nitrogen heterocycles present interesting pharmaceutical activities. Thus, 6,11-dihydro-5*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridine (**1**) and *N*-substituted benzo[5,6]cyclohepta[1,2-*b*]indole (**2**) are potent antitumoral agents[1,2] against L1210 murine leukemia and HT29 cell lines, while piperazinyl and piperidinyl derivatives inhibit the farnesyl protein transferase (FPT).[3]



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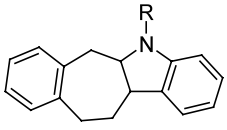

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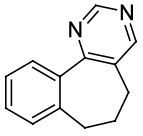
Thus, the preparation of related compounds with different nitrogen rings presents a great interest. Particularly, the introduction of a pyrimidine ring leads to an interesting class of heterocycles, the corresponding 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines (**3**).



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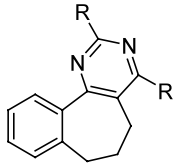
Among these, only the 4-substituted derivatives are known; they show activity on blood platelet aggregation and are also investigated for their effect on reserpine-induced hypothermia.[4] We report here the easy one-pot synthesis of 2,4-disubstituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines (**4**), which have a pyrimidine nucleus fused to the benzocycloheptabicycle.



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The reaction of ketones with nitriles in the presence of triflic anhydride[5,6] allowed us to prepare the target molecules. Hence, the treatment of the commercially available 1-benzosuberone (**5**) with different nitriles and triflic anhydride (Scheme 1) provided easily the new heterocycles in good yield. The mechanism of this reaction involves the formation of a trifliloxycarbenium ion which is trapped by the nitrile, forming a nitrilium ion. A second molecule of nitrile reacts with the intermediate nitrilium ion to give the corresponding pyrimidine, after elimination of TfOH, cyclization and loss of a proton.[5] The formation of a minor amount (5–10%) of a side product such as the trisubstituted 1,3,5-triazine (**6**) corresponding to the trimerization of the aromatic nitrile was also observed.[7]

It is important to note that the reaction of 1-benzosuberone (**5**) with methylthiocyanate affords the 2,4-bis(thiomethyl) pyrimidines (**4c**). These compounds

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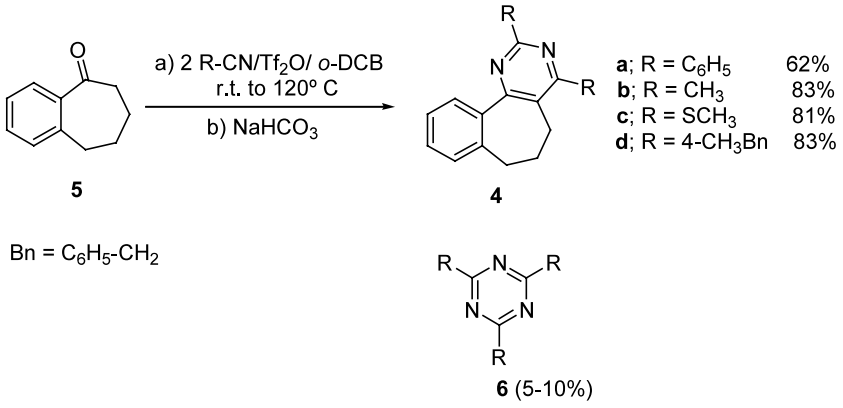

Scheme 1. Synthesis of 2,4-diaryl substituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines **4**.

open an important synthetic route to other interesting pyrimidine derivatives on account of the easy conversion of the thiomethyl group into other interesting groups such as methylsulphonyl and amino groups.[8] The synthetic procedure and the characterization data for the new substances are reported.[9,10]

In summary, we have prepared a new class of heterocycles from easily available starting materials. On the other hand, we have demonstrated the versatility of the reaction of ketones and nitriles in the presence of triflic anhydride.

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9. General procedure for the preparation of **4**: To a solution of 0.2 g (1.25 mmol) of **5** in 25 mL of *o*-DCB is added dropwise a solution containing 2.50 mmol of the corresponding nitrile and 1.25 mmol of Tf_2O in 15 mL of *o*-DCB. The mixture is stirred overnight and heated at 120°C during 2 h. The reaction mixture is carefully hydrolyzed with $NaHCO_3$ and the organic layer extracted with dichloromethane. After drying and evaporation of the solvent, the residue is recrystallized in the appropriate solvent.
10. Characterization data for **4a**: mp 152–153°C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (t, 2H, $J=6.7$ Hz, CH_2), 2.56 (q, 2H, $J=6.7$ Hz, CH_2), 2.77 (t, 2H, $J=6.7$ Hz, CH_2), 7.34 (m, 1H), 7.51 (m, 8H), 7.76 (m, 2H), 8.01 (m, 1H), 8.64 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$):26.16, 31.73, 34.15 (CH_2), 126.98, 127.19, 128.25, 128.35, 128.39, 128.63, 129.21, 129.28, 129.53, 130.16, 137.95, 138.79, 138.81, 140.19, 161.68, 167.26, 127.26 (C arom.); MS (EI, 70 eV) *m*/*z* 348 ($M^{\bullet+}$, 74), 347 (100). Anal. calcd for $C_{25}H_{30}N_2$: C, 86.18; H, 5.79; N, 8.04%. Found: C, 86.75; H, 5.99; N, 8.20. Characterization data for **4b**: mp 73–74°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): 2.20 (m, 2H), 2.49 (m, 4H), 2.57 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 7.22 (m, 1H), 7.77 (m, 2H), 7.72 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): 21.94, 26.01 (CH_3), 24.77, 31.33, 32.12 (CH_2), 126.63, 126.97, 128.58, 128.60, 129.77, 138.44, 138.68, 163.78, 165.03, 165.32 (C arom.); MS (EI, 70 eV) *m*/*z*: 288 ($M^{\bullet+}$, 100), 273 (53), 255 (53). Anal. calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49%. Found: C, 79.89; H, 6.98; N, 12.77. Characterization data for **4c**: mp 65–66°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): 2.22 (m, 2H), 2.52 (m, 2H), 2.61 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 7.22 (m, 1H), 7.37 (m, 2H), 7.74 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): 13.02, 14.30 (SCH_3), 24.79, 31.64 (CH_2), 123.90, 126.89, 128.80, 128.99, 130.02, 137.71, 140.08, 162.49, 168.34, 168.74 (C arom.); MS (EI, 70 eV) *m*/*z* 288 ($M^{\bullet+}$, 100), 273 (53), 255 (55). Anal. calcd for $C_{15}H_{16}N_2S_2$: C, 62.67; H, 5.59; N, 9.71%. Found: C, 62.88; H, 5.11; N, 10.03. Characterization data for **4d**: undistillable oil. ^{1}H NMR (300 MHz,

$CDCl_3$): 1.88 (m, 2H), 2.32 (s, 3H, CH_3), 2.34 (m, s, CH_3), 4.19 (s, 2H), 4.32 (s, 2H), 7.14 (m, 7H), 7.35 (m, 4H), 7.72 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): 21.01, 21.06 (CH_3), 24.68, 31.20, 32.06 (CH_2), 41.30, 45.32 (Ar-CH_2-Ar), 126.89, 127.30, 128.49, 128.57, 128.90, 128.98, 129.11, 129.21, 129.79, 135.69, 135.75, 135.97, 136.25, 138.54, 139.78 (C arom.); MS (EI, 70 eV) m/z 404 ($M^{\bullet+}$, 100), 389 (24), 299 (27). Anal. calcd for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.92%. Found: C, 85.63; H, 7.06; N, 7.04.