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ADDITION OF PHENYLMAGNESIUM BROMIDE TO AN AMINO-CYANO-THIOPHENE

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We report the isolation, structure, and reactivity of an unexpected intermediate arising from the reaction of phenylmagnesium bromide with an amino-cyano-thiophene.

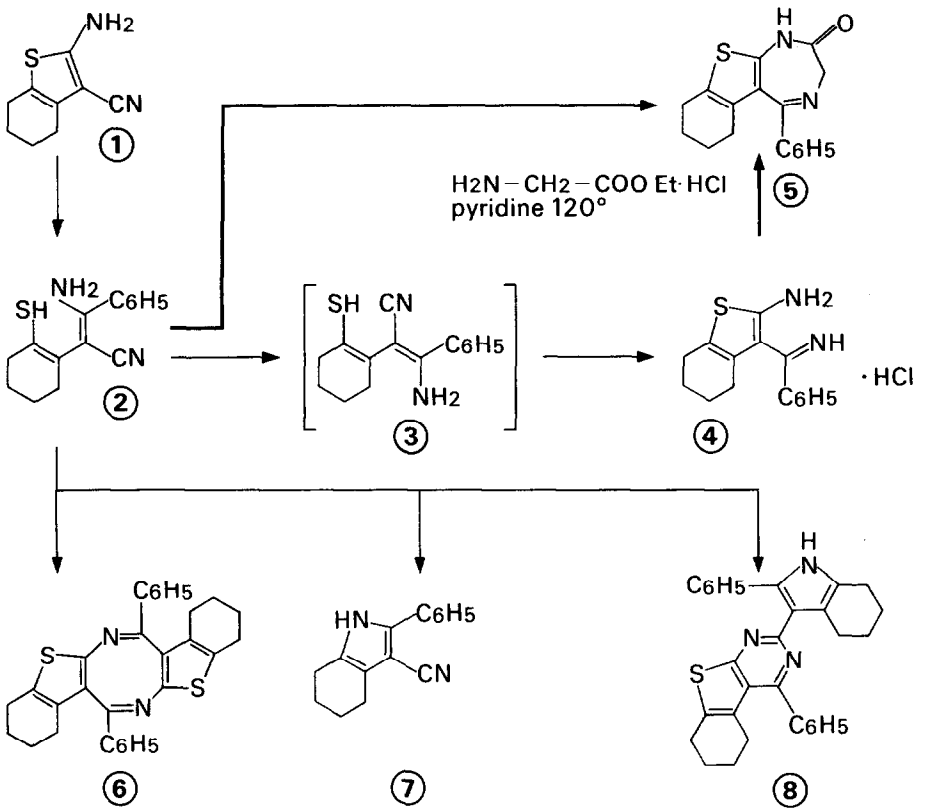
When 0,3 moles of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (①)[1] were added to 1,5 moles of phenylmagnesium bromide in refluxing tetrahydrofurane*, the resulting solution refluxed for 24 hours and finally poured into a stirred mixture of saturated aqueous ammonium chloride and ether/hexane (1:1) at -10°, a yellow crystalline solid precipitated : mp (CH_2Cl_2/hexane) 118-120° dec. with evolution of H_2S; $\nu_{max}^{(CH_2Cl_2)}$ cm^{-1} : 3480 and 3390 (NH_2), 2920, 2200 (CN), 1620; λmax (MeOH, fresh solution) nm (log ε) : 294 (3,79), δ($CDCl_3$) ppm : 1,55 6H-m, 2,50 2H-m, 6,20-7,20 3H-m very broad, exchangeable, 7,33 5H-s; m/e : 256, 239, 227, 104, 77, 51; pK (methylcellosolve/H_2O = 8:2) a) titrated with 0,1-N NaOH : 9,95, b) titrated with 0,1-N HCl : 7,36; analysis correct for $C_{15}H_{16}N_2S$; yield 70 %.

These data are in accordance with structure ② for which further evidence was obtained as follows :

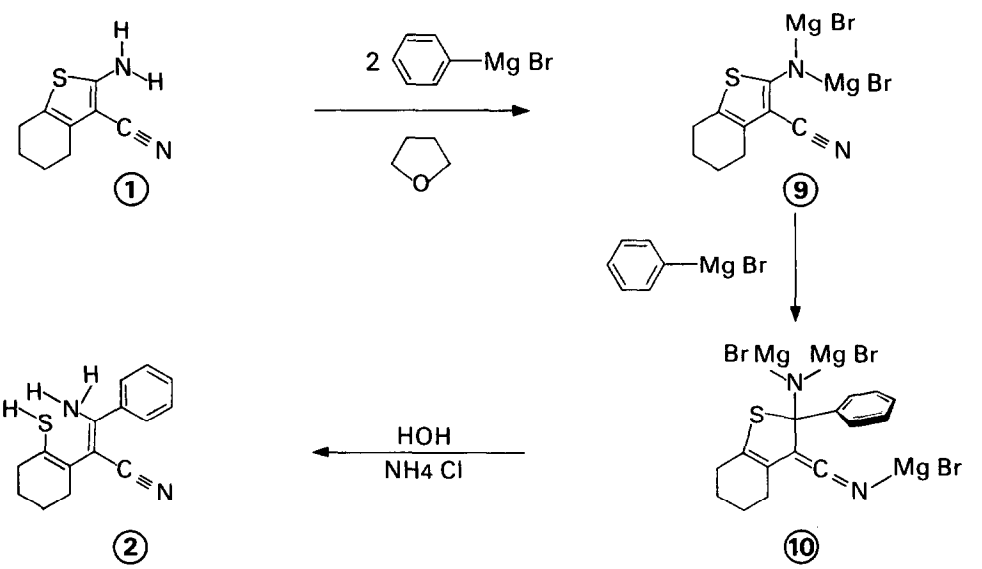
A positive test with sodium nitroprusside was indicative of a sulfhydryl group. The characteristic ir-nitrile band as well as the uv-maximum at 294 nm of ② disappeared

* No reaction was observed when ether was used as solvent.

scheme I



scheme II



gradually when a methanolic solution was kept at 20° for 20 hours. The resulting imine ④ was converted to its hydrochloride in 80 % yield : mp (ethanol) 268-273° dec.; $\nu_{max}^{(KBr)}$ cm^{-1} : 3500, 3300 and 3150 (NH_2,NH), 2900, 1660, 1620, 1470, 1450; $\lambda_{max}^{(MeOH)}$ ($\log\varepsilon$): 270 (4,13), 440 (3,59), δ(DMSO-d_6) ppm : 1,60 6H-m, 2,50 2H-m, 7,2-8,4 3H-m broad, exchangeable, 7,65 5H-s broad; m/e : 256, 255, 227, 104; pK (methylcellosolve/H_2O = 8:2) titrated with 0,1-N tetramethylammonium hydroxide : 7,33; analysis correct for $C_{15}H_{17}ClN_2S$.

The imine ④ yielded 60 % 1,3,6,7,8,9-hexahydro-5-phenyl-2H-[1]benzothieno[2,3-e][1,4]diazepin-2-one (⑤)[2)3)] after condensation with glycine ethylester hydrochloride in refluxing pyridine. Unter the same conditions ⑤ was also obtained directly from ②.

Thermolysis of ② at 200° for 15 minutes gave rise to three characteristic products which were separated by column chromatography (silicagel, methylene chloride).

The first compound (yield 22 %) showed mp (benzene/ethanol) 300-305°; $\nu_{max}^{(KBr)}$ cm^{-1} : 2960, 1620, 1340, 1280, 1120, 1030, 877, 768; $\lambda_{max}^{(MeOH)}$ nm ($\log\varepsilon$) : 274 (4,18); δ($CDCl_3$) ppm : 1,5-2,0 12H-m broad, 2,6-3,0 4H-m broad, 7,4 and 7,8 10H-m; m/e : 478, 374, 346, 318, 104, 77; analysis correct for $C_{30}H_{26}N_2S$. Structure ⑥ fits these data.

The second substance (yield 12 %) was identified as the 2-phenyl-3-cyano-4,5,6,7-tetrahydroindole ⑦ : mp (CH_2Cl_2/hexane) 200-202°; $\nu_{max}^{(CH_2Cl_2)}$ cm^{-1} : 3450, 3300, 2220 (CN), 1610, 1540, 1500; $\lambda_{max}^{(MeOH)}$ nm ($\log\varepsilon$) : 308 (4,21); δ($CDCl_3$) ppm : 1,4-1,8 4H-m broad, 2,2-2,4 4H-m broad, 7,2 and 7,5 5H-m, 8,7 1H-s broad, exchangeable; m/e : 222, 194, 104, 77, 63, 51, 39; analysis correct for $C_{15}H_{14}N_2$. The same compound ⑦ was also obtained in 20 % yield when crude ② was subjected to chromatography on silicagel.

Structure ⑧ was assigned to the third component (yield 13 %) on the basis of the following data : mp (CH_2Cl_2/hexane) 221-222°; $\nu_{max}^{(CH_2Cl_2)}$ cm^{-1} : 3400, 2900, 1600, 1520, 1490, 1175; $\lambda_{max}^{(MeOH)}$ nm ($\log\varepsilon$) : 239 (4,45), 272 (4,38); δ($CDCl_3$) ppm : 1,5-3,0 16H-m

broad, 7,15-7,40 10H-m, 7,97 1H-s broad, exchangeable; m/e : 461, 433, 432, 230 1/2, 104, 77; analysis correct for $C_{30}H_{27}N_3S$. This product seems to arise from the condensation of the nitrile (7) with the initially formed imine (4).

Scheme II illustrates a possible pathway for the reaction of the cyano-amine (1) with an excess of phenylmagnesium bromide. The initially formed organomagnesium complex (9)* undergoes 1,4-addition of phenylmagnesium bromide to give (10). The allylic sulphur-carbon bond of the latter is readily broken upon hydrolysis to afford (2).

The stability of (2) in the crystalline state may be attributed to hydrogen bonding between the amino and the sulfhydryl group. This bond is broken by protic and polar solvents allowing rotation about the central carbon-carbon single bond of (2). The resulting rotamer (3) (scheme I) finally undergoes ring closure to the imine (4).

* A Zerewitinoff determination indicated two active hydrogens in (1).

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