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NOVEL APPROACH TO SYNTHESIS OF TETRAHYDROBENZO[*b*]THIENO[3,2-*d*]AZOCINES

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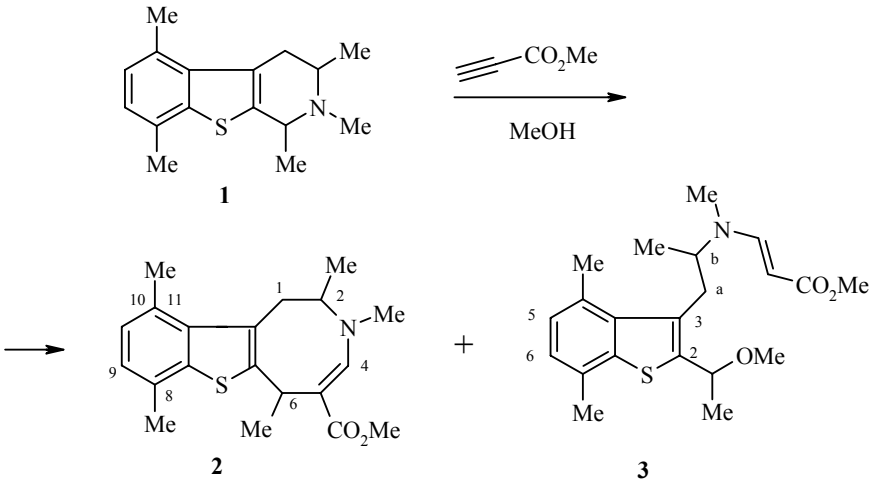
In developing a strategy for synthesis of condensed azocines based on tandem transformations of the tetrahydropyridine ring in annelated tetrahydropyridines when treated with activated alkynes, we have shown that the thiophene ring inhibits these transformations [1]. Thus when ethyl propiolate reacts with 5-ethyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine, we see only elimination of the N-ethyl radical and formation of N-(2-ethoxycarbonylvinyl)tetrahydrothienopyridine. N-*o*-chlorobenzyltetrahydrothieno[3,2-*c*]pyridine (ticlid) and its 2-formyl derivative behave analogously when treated with activated alkynes, where (according to our unpublished data) elimination of the *o*-chlorobenzyl radical also occurs. We showed that tetrahydrobenzo[*b*]thieno[2,3-*c*]pyridine **1** reacts with methyl propiolate in methanol, forming a mixture of benzothienoazocine **2** and methyl (*E*)-3-[2-[2-(1-methoxyethyl)-4,7-dimethyl-1-benzothiophen-3-yl]-1-methylethyl(methyl)amino]-2-propenoate (**3**) in 1:5 ratio. The reaction probably occurs analogously to the tandem transformations we described for tetrahydro-β-carbolines in [2]. Compound **3** was isolated as a mixture of diastereomers in ~1:7 ratio.

When treated with aluminum chloride, the methoxyethyl substituted compounds **3** are converted to the benzothienoazocines **2**. Thus we have developed a novel approach to synthesis of benzothienoazocines.



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The ^{1}H NMR spectra were taken in $CDCl_3$ (400 MHz), internal standard TMS.

Methyl 2,3,6,8,11-Pentamethyl-1,2,3,6-tetrahydrobenzo[*b*]thieno[3,2-*d*]azocine-5-carboxylate (2), Methyl (*E*)-3-[2-[2-(1-Methoxyethyl)-4,7-dimethyl-1-benzothiophen-3-yl]-1-methylethyl(methyl)amino]-2-propenoate (3). Methyl propiolate (0.20 g, 2.40 mmol) was added to a solution of benzothienopyridine **1** (0.52 g, 1.10 mmol) in dry methanol (10 ml). The reaction mixture was stirred at room temperature (monitored by TLC: Alufol plates, ethylacetate–hexane, 1:3). The solvent was evaporated and the residue was chromatographed on a column with Al_2O_3 (hexane–ethyl acetate, 50:1). Azocine **2** (17 mg) and compound **3** (83 mg) were successively eluted.

Compound 2. White crystals; mp 196-198°C, R_f 0.76 (Alufol plates, ethyl acetate–hexane, 1:3). Yield 4.4%. Mass spectrum, *m*/*z* (I_{rel}, %): 344 $[M]^+$ (10), 343 (47), 328 (11), 312 (9), 286 (7), 285 (6.5), 284 (31), 272 (8), 254 (6), 253 (7), 242 (14), 229 (13), 228 (18), 227 (13), 226 (11), 225 (6), 214 (8), 213 (17), 212 (17), 211 (13), 204 (5), 302 (15), 202 (100), 201 (6), 199 (7), 198 (7), 197 (8), 187 (7), 185 (6), 42 (13). IR spectrum, ν, cm^{-1}: 1607 (C=C), 1668 ($COOCH_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (1H, s, H-4); 7.00 (1H, d, *J* = 7.3, H-9); 6.92 (1H, d, *J* = 7.3, H-10); 4.82 (1H, q, *J* = 7.2, H-6); 4.55 (1H, m, H-2); 3.75 (1H, s, OCH_3); 3.65 (1H, dd, *J* = 12.7, *J* = 16.9, H*a*-1); 3.20 (1H, dd, *J* =2.9, *J* = 16.9, H*e*-1); 2.84 (3H, s, N–CH_3); 2.82 (3H, s, 8-CH_3); 2.40 (3H, s, 11-CH_3); 1.65 (3H, d, *J* = 7.2, 6-CH_3); 1.40 (3H, d, *J* = 6.6, 2-CH_3). Found, %: C 69.87; H 7.21; N 4.10. $C_{20}H_{25}NO_2S$. Calculated, %: C 69.93; H 7.34; N 4.08.

Compound 3. White crystals; mp 82-84°C, R_f 0.35 (Alufol plates, ethyl acetate–hexane, 1:3). Yield 20%. Mass spectrum, *m*/*z* (I_{rel}, %): 375 $[M]^+$ (5), 143 (8), 142 (100), 84 (7), 82 (7), 59 (14), 42 (16). IR spectrum, ν, cm^{-1}: 1604 (C=C), 1682 ($COOCH_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.54 (0.13H, d, *J* = 12.8, N–$\underline{CH}$=CH_{min}); 7.43 (0.87H, d, *J* = 12.9, N–$\underline{CH}$=CH_{maj}); 7.05 (1H, d, *J* = 7.3, H-6); 7.00 (1H, d, *J* = 7.3, H-5); 4.7 (1H, m, $\underline{CH}$–O–CH_3); 4.57 (0.13H, d, *J* = 12.8, N–CH=$\underline{CH}_{min}$); 4.55 (0.87H, d, *J* = 12.9, N–CH=$\underline{CH}_{maj}$); 3.65 (0.39H, s, O–$CH_{3\ min}$); 3.64 (2.61H, s, O–$CH_{3\ maj}$); 3.60 (1H, m, H-β); 3.29 (0.39H, s, O–$CH_{3\ min}$); 3.28 (2.61H, s, O–$CH_{3\ maj}$); 3.17 (2H, m, α-CH_2); 2.7 (6H, s, 4-CH_3+7-CH_3); 2.5 (3H, s, N–CH_3); 1.56 (0.39H, d, *J* = 6.4, $\underline{CH_3}$–CH–O–$CH_{3\ min}$); 1.52 (2.61H, d, *J* = 6.2, $\underline{CH_3}$–CH–O–$CH_{3\ maj}$); 1.32 (2.61H, d, *J* = 6.7, β-$CH_{3\ maj}$); 1.25 (0.39H, d, *J* = 6.7, β-$CH_{3\ min}$). Found, %: C 67.05; H 7.65; N 3.78. $C_{21}H_{29}NO_3S$. Calculated, %: C 67.17; H 7.78; N 3.73.

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