Chemistry of Heterocyclic Compounds, Vol. 43, No. 11, 2007

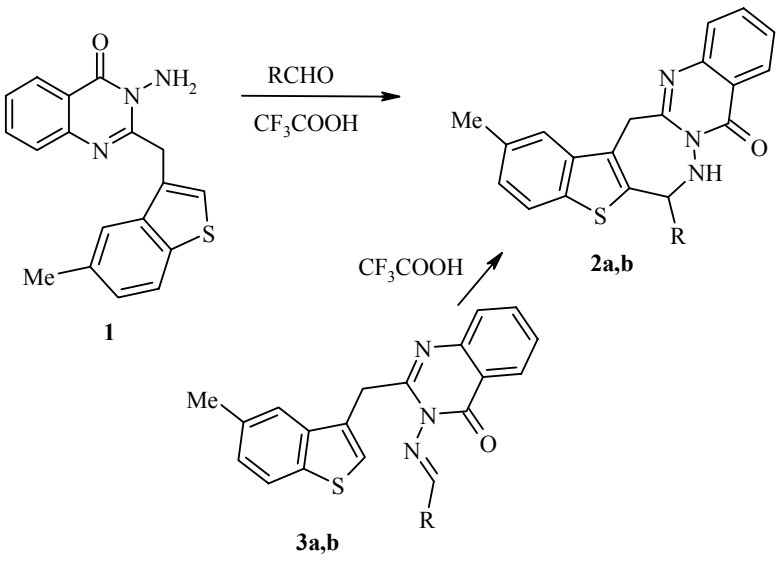
NEW STRATEGY FOR THE SYNTHESIS OF TETRAHYDROBENZOTHIENO-[1,2]DIAZEPINES

A. S. Tolkunov and S. L. Bogza

Keywords: 3-amino-2-(3-benzo[*b*]thienylmethyl)quinazolines-4(3H)-one, tetrahydrobenzothieno-[2',3':4,5][1,2]diazepino[7,1-*b*]quinazolin-9-one, Pictet-Spengler reaction, cyclization.

Derivatives of 2,3-benzodiazepine display considerable biological activity and are under extensive investigation [1]. Condensed benzodiazepines are less available and the methods for their synthesis are based on adding on a heterocycle to one of the edges of the benzodiazepine system [2] or expansion of the pyran ring in heterofused isocoumarins [3].

The heterocyclic [5H]benzothieno[2,3-*e*]diazepine system was first prepared in the recyclization of 1,3-disubstituted benzothieno[2,3-*c*]pyrilium salts by hydrazine hydrate [4]. The reaction of 3-amino-2-(5-methyl-3-benzo[*b*]thienylmethyl)quinazolin-4(3H)-one (**1**) with aromatic aldehydes under conditions of the Pictet-Spengler reaction was used to obtain derivatives of a new heterocyclic system, namely, tetrahydro-benzothieno[2',3':4,5][1,2]diazepinoquinazolines **2a,b**. The yields of products **2a**,**b** were 57-65%. The reaction



2, **3 a** R = 4-$MeOC_6H_4$, **b** R = 4-ClC_6H_4

L. M. Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, 83114 Donetsk; e-mail: s_tolkunov@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1740-1741, November, 2007. Original article submitted July 12, 2007.

0009-3122/07/4311-1485

proceeds through intermediate formation of Schiff bases **3**, which was confirmed by the cyclization of azomethine **3b** to give benzothienoquinazolinodiazepine **2b** under conditions of the basic reaction. The structure of benzothienodiazepines **2a,b** was demonstrated using ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **2a**,**b** have characteristic doublets for the CH_2 group of the diazepine ring at 4.40-4.85 ppm with coupling constant 14-15 Hz, which indicates nonplanar structure of the diazepine ring.

The ^{1}H NMR spectra were taken on a Varian Gemini 200 spectrometer at 200 MHz in DMSO-d_6 at 50°C with TMS as the internal standard.

General Procedure. A mixture of amine **1** (0.64 g, 2 mmol), an equivalent amount of an aromatic aldehyde (or 2 mmol Schiff base **3a** or **3b**), and trifluoroacetic acid (4 ml) was heated at reflux for 5 h. Trifluoroacetic acid was removed at reduced pressure and 10 ml 5% aqueous ammonia was added to the residue. The crystals were filtered off, washed with water, and recrystallized from DMF–acetonitrile.

6-(4-Methoxyphenyl)-2-methyl-6,7,8,9-tetrahydrobenzothieno[2'3':4,5][1,2]diazepino[7,1-b]quinazolin-9-one (2a) was obtained in 57% yield; mp 219-220°C (DMF–acetonitrile). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 3.78 (3H, s, OCH_3); 4.39 (1H, d, J = 14.8, CH_2); 4.85 (1H, d , J = 14.8, CH); 5.60 (1H, s, CH); 6.86-7.74 (6H, m, H_{arom}); 7.61 (2H, d, J = 8.1, H_{arom}-2',6'), 7.75 (2h,d, J = 8.1, H_{arom}-3',5'); 8.09 (1H, d, J = 7.7, H_{arom}-10). Found, %: C 71.05; H 4.82; N 9.56; S, 7.29. $C_{26}H_{21}N_3O_2S$. Calculated %: C 71.19; H 4.91; N 9.42; S 7.12.

6-(4-Chlorophenyl)-2-methyl-6,7,8,15-tetrahydrobenzothieno[2',3':4,5][1,2]diazepino[7,1-b]quinazolin-9-one (2b) was obtained in 65% yield; mp 232°C (DMF–acetonitrile). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 4.42 (1H,d, J = 14.1, CH_2); 4.85 (1H, d, J = 14.1, CH_2); 5.73 (1H, s, CH); 7.15-7.79 (10H, m, H_{arom}); 8.10 (1H,d, J = 6.7, H_{arom}10). Found, %: C 67.78; H 4.17; Cl 7.81; N 9.38; S 7.12. $C_{25}H_{18}ClN_3OS$. Calculated, %: C 67.64; H 4.09; Cl 7.99; N 9.46; S 7.22.

REFERENCES

1. E. J. Horvath, K. Horvath, T. Hamori, M. I. K. Fekete, S. Solyom, and M. Palkovits, *Progress in Neurobiology*, **60**, 309 (2000).
2. A. Gizella, S. Solyom, E. Csuzdi, P. Bersenyi, I. Ling, I. Tarnawa, T. Hamori, I. Pallagi, K. Horvath, F. Andrassi, and G. Kapus, *Bioorg. Med. Chem.*, **8**, 2127 (2000).
3. J. Dusemund, *Arch. Pharm.*, **316**, No. 2, 110 (1983).
4. S. V. Tolkunov, S. Yu. Suykov, M. Yu. Zubritsky, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1137 (1998). [*Chem. Heterocycl. Comp.*, **34**, 983 (1998)].