# New synthesis of 1,4-benzothiazepin-5-ones ✽

*M. A. Mironov,* M. N. Ivantsova, M. I. Tokareva, V. S. Mokrushin*

*Urals State Technical University,*
*19 ul. Mira, 620002 Ekaterinburg, Russian Federation.*
*Fax: +7 (343) 375 41 35. E-mail: mir@htf.ustu.ru*

A new convenient method for the synthesis of 1,4-benzothiazepin-5-ones by a one-pot procedure including condensation of thiosalicylic acid with chloroacetone and the reaction of the resulting 2-(acetoxythio)benzoic acid without isolation with primary amines and isocyanides is proposed. This method can be used for the combinatorial search of compounds with biological activities in the 1,4-benzothiazepine series.

**Key words:** Ugi reaction, isocyanides, 1,4-benzothiazepines, combinatorial synthesis.

In recent years, the number of publications devoted to the preparation of heterocyclic compounds by multicomponent reactions has sharply increased.[1] This is due to obvious advantages of one-pot synthetic strategy, which completely eliminates the losses during isolation and purification of intermediate products. In addition, this approach allows one to vary simultaneously several side substituents, which opens up prospects for highly efficient screening. The greatest diversity of structures is provided by a combination of a multicomponent reaction and intramolecular cyclization.[2] A combination of intramolecular reactions with the four-component Ugi condensation proved to be especially fruitful.[3] We first used this approach to synthesize 1,4-benzothiazepin-5-one derivatives.[4] Benzothiazepines exhibit a broad spectrum of biological activities (for example, they act as calcium channel-blocking agents[5] and inhibitors of some enzymes[6]); this has stimulated studies dealing with the combinatorial synthesis of these compounds based on a solid-state strategy.[7,8] The purpose of this work was to develop a combinatorial liquid-phase synthesis of 1,4-benzothiazepin-5-one derivatives that would be free from the drawbacks inherent in solid-state methods (large excess of the reagents, the use of expensive polymeric materials).[9]

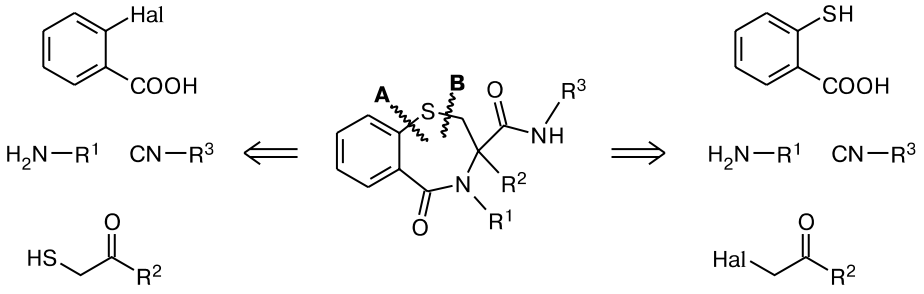
## Results and Discussion

There are two basically different approaches to the synthesis of 1,4-benzothiazepin-5-ones using the Ugi reaction (Scheme 1).

Path **A** implies intramolecular arylation of the mercapto group; therefore mercapto ketone, α-halobenzoic acid, amine, and isocyanide should be the components of the Ugi reaction. In the other case (path **B**), the target heterocycle is formed upon intramolecular alkylation, and a different set of components can be used, namely, haloketone, thiosalicylic acid, amine, and isocyanide. Most important was the possibility of conducting this synthesis in one step by direct mixing of the initial components. Due to the absence of any published data, it was necessary to find out whether reagents with unprotected mecrapto groups can be used in the Ugi reaction. Two control experiments were carried out under conditions standard for the Ugi reaction (equimolar ratio of all reactants, concentrated methanolic solution, room temperature); the reactants were selected in such a way as to exclude intramolecular cyclization (Scheme 2).

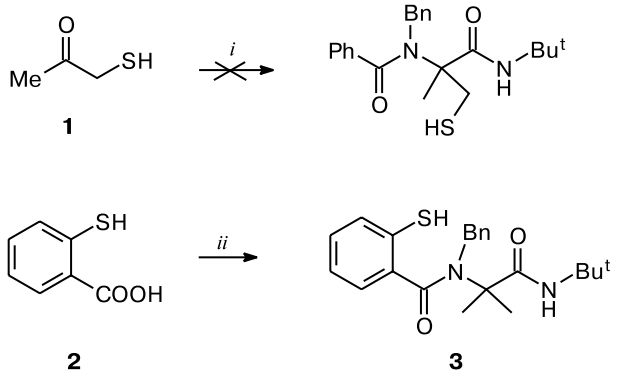
It was found that with mercaptoketone **1** as the component, the Ugi reaction proceeds with lower selectivity

**Scheme 1**




Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1183—1187, June, 2004.

**Scheme 2**



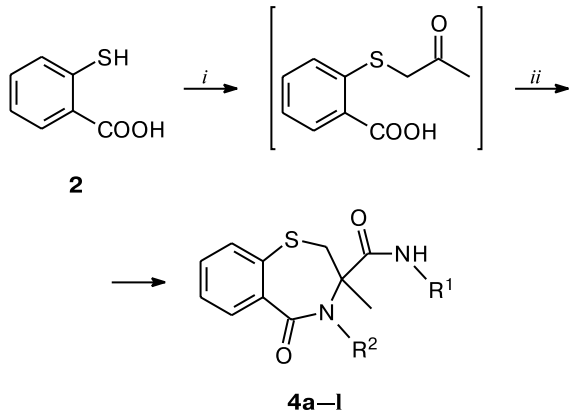
*i*. $H_2N$—Bn, CN—$Bu^t$, PhCOOH; *ii*. $H_2N$—Bn, CN—$Bu^t$, $Me_2CO$.

and gives a complex mixture of products. Apparently, in this case, the competing Asinger condensation predominates.[3] When thiosalicylic acid **2** is condensed with acetone, *tert*-butyl isocyanide, and benzylamine, no by-products are detected (see Scheme 2). The structure of compound **3** was proved by $^1$H NMR spectroscopy, all signals being assigned by analogy with published data.[10] The spectrum exhibited a signal for the free mercapto group (3.83 ppm), while signals for the dimer of compound **3** were absent. Thus, for the synthesis of target 1,4-benzothiazepin-5-ones, we chose path **B**. However, the replacement of acetone by chloroacetone did not result in the formation of 1,4-benzothiazepin-5-ones. The reaction gave colored polymeric compounds, whose formation can be attributed to polycondensation of the open product of the Ugi reaction. This unfavorable reaction route may be facilitated by high concentrations of the starting reactants (10—20% solutions). However, the use of dilute (1—2%) solutions did not furnish the target products, nor did the addition of bases (triethylamine or potash) to the reaction mixture for increasing the alkylation rate of the mercapto group.

In view of the results obtained, successive condensation of four reactants was chosen for the synthesis of the target products. First, thiosalicylic acid was alkylated with chloroacetone in a concentrated methanolic solution in the presence of a base and then the other components, amine and isocyanide, were added to the same solution (Scheme 3).

The reaction products were purified by parallel flash chromatography. This variant rules out the intermolecular alkylation and allows one to reach high yields of 1,4-benzothiazepin-5-ones (up to 90%). It is noteworthy that cyclization of keto acids is a well-known and widely used version of the Ugi reaction.[11] However, we were the first to apply the one-pot strategy that includes the preparation and further cyclization of a keto acid. The efficiency of this method is not inferior to that of the direct

**Scheme 3**



*i*. Cl, $K_2CO_3$. *ii*. $R^1$—NC, $R^2$—$NH_2$.

| **4** | $R^1$ | $R^2$ |
|---|---|---|
| **a** | 4-$Me_2NC_6H_4$ | Bn |
| **b** | 4-$Me_2NC_6H_4$ | Furfuryl |
| **c** | 4-$Me_2NC_6H_4$ | 4-$MeOC_6H_4CH_2$ |
| **d** | 2,4-$MeOC_6H_3$ | $PyCH_2$ |
| **e** | 2,4-$MeOC_6H_3$ | Furfuryl |
| **f** | 2,4,6-$MeC_6H_2$ | 4-$CF_3C_6H_4CH_2$ |
| **g** | 2,4,6-$MeC_6H_2$ | Cyclopropyl |
| **h** | Ad | $PyCH_2$ |
| **i** | Ad | Cyclopropyl |
| **j** | 4-Morpholinyl-$C_6H_4$ | Bn |
| **k** | 4-Morpholinyl-$C_6H_4$ | 4-$CF_3C_6H_4CH_2$ |
| **l** | 4-Morpholinyl-$C_6H_4$ | 4-$MeOC_6H_4CH_2$ |

multicomponent synthesis based on mixing of all components.

To elucidate the potential provided by the variation of the side substituents, we synthesized a series of compounds **4a—l** (see Scheme 3). The selection of isocyanides corresponded to general rules applicable to other variants of the Ugi reaction. The use of isocyanides with electron-releasing substituents results in high yields of the target products, while electron-withdrawing substituents decrease the reactivity of isocyanides. For example, we were unable to prepare the 1,4-benzothiazepin-5-one from 4-nitrophenyl isocyanide. The structures of the compounds **4** formed can be confirmed without difficulty, because numerous literature analogies are available.[7,8,11] The mass spectra of 1,4-benzothiazepin-5-ones contain molecular ion peaks with relatively low (1—10%) intensity, which correspond to the calculated mass. The $^1$H NMR spectra show signals for the side groups (amine and isocyanide residues) and characteristic signals of the thiazepine ring (two doublets for the $CH_2$ group in the regions of 4.5—4.0 and 3.0—2.2 ppm with a spin-spin coupling constant of 12—14 Hz).

The transformation we describe is a variant of four-component condensation, which obeys the regularities established back in classical Ugi´s works.[3] Indeed, the

**Table 1.** $^1$H NMR (DMSO-$d_6$) and mass spectra (EI, 70 eV) of 1,4-benzothiazepin-5-ones **4a—l**

| Compound | $^1$H NMR spectrum (δ, *J*/Hz) | Mass spectrum, *m/z* ($I_{rel}$ (%)) |
|---|---|---|
| **4a** | 9.35 (br.s, 1 H, NH); 7.59 (d, 2 H, Ph, *J* = 7.3); 7.37—7.13 (m, 7 H, Ph and $C_6H_4S$); 6.75 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.2); 6.49 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.2); 5.92 (d, 1 H, $NCH_2Ph$, *J* = 16.2); 4.37 (d, 1 H, $NCH_2Ph$, *J* = 16.2); 4.13 (d, 1 H, $SCH_2$, *J* = 11.9); 2.86 (s, 6 H, 2 Me); 2.27 (d, 1 H, $SCH_2$, *J* = 11.9); 1.61 (s, 3 H, Me) | 445 $[M]^+$ (7), 282 (100), 191 (17), 177 (10), 91 (85) |
| **4b** | 9.31 (br.s, 1 H, NH); 7.51 (dd, 1 H, $C_4H_3O$, *J* = 1.8, *J* = 0.8); 7.29—7.13 (m, 4 H, $C_6H_4S$); 6.77 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.2); 6.49 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.2); 6.45 (d, 1 H, $C_4H_3O$, *J* = 3.2); 6.39 (dd, 1 H, $C_4H_3O$, *J* = 3.2, *J* = 1.8); 5.70 (d, 1 H, $NCH_2Het$, *J* = 16.4); 4.40 (d, 1 H, $NCH_2Het$, *J* = 16.4); 4.19 (d, 1 H, $SCH_2$, *J* = 12.2); 2.86 (s, 6 H, 2 Me); 2.53 (d, 1 H, $SCH_2$, *J* = 12.2); 1.72 (s, 3 H, Me) | 435 $[M]^+$ (8), 272 (100), 271 (20), 203 (34), 69 (21) |
| **4c** | 9.29 (br.s, 1 H, NH); 7.50 (d, 2 H, $C_6H_4OMe$, *J* = 8.5); 7.35—7.15 (m, 4 H, $C_6H_4S$); 6.87 (d, 2 H, $C_6H_4OMe$, *J* = 8.5); 6.76 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.0); 6.49 (d, 2 H, $C_6H_4NMe_2$, *J* = 9.0); 5.83 (d, 1 H, $NCH_2Ar$, *J* = 15.9); 4.31 (d, 1 H, $NCH_2Ar$, *J* = 15.9); 4.11 (d, 1 H, $SCH_2$, *J* = 12.2); 3.78 (s, 3 H, OMe); 2.27 (d, 1 H, $SCH_2$, *J* = 12.2); 1.61 (s, 3 H, Me) | 475 $[M]^+$ (6), 460 (5), 312 (100), 284 (71), 121 (92), 107 (16) |
| **4d** | 8.80 (d, 1 H, Py, *J* = 1.8); 8.54 (dd, 1 H, Py, *J* = 4.7, *J* = 1.8); 8.34 (br.s, 1 H, NH); 8.10 (d, 1 H, Py, *J* = 4.7); 7.46 (dd, 1 H, Py, *J* = 4.8, *J* = 4.7); 7.35—7.19 (m, 4 H, $C_6H_4S$); 6.92 (d, 1 H, $C_6H_3(OMe)_2$, *J* = 8.8); 6.57 (d, 1 H, $C_6H_3(OMe)_2$, *J* = 2.6); 6.32 (dd, 1 H, $C_6H_3(OMe)_2$, *J* = 8.8, *J* = 2.6); 5.14 (d, 1 H, $NCH_2Py$, *J* = 16.3); 5.02 (d, 1 H, $NCH_2Py$, *J* = 16.3); 4.20 (d, 1 H, $SCH_2$, *J* = 12.9); 3.83 (s, 3 H, OMe); 3.70 (s, 3 H, OMe); 2.94 (d, 1 H, $SCH_2$, *J* = 12.9); 1.56 (s, 3 H, Me) | 463 $[M]^+$ (12), 449 (10), 283 (89), 269 (27), 191 (35), 92 (100) |
| **4e** | 8.26 (br.s, 1 H, NH); 7.52 (dd, 1 H, $C_4H_3O$, *J* = 1.8, *J* = 0.8); 7.24—7.08 (m, 4 H, $C_6H_4S$); 7.03 (d, 1 H, $C_6H_3(OMe)_2$, *J* = 8.8); 6.48—6.44 (m, 3 H, $C_6H_3(OMe)_2$ and $C_4H_3O$); 6.24 (dd, 1 H, $C_6H_3(OMe)_2$, *J* = 8.8, *J* = 2.6); 5.05 (d, 1 H, $NCH_2Het$, *J* = 16.5); 4.96 (d, 1 H, $NCH_2Het$, *J* = 16.5); 4.24 (d, 1 H, $SCH_2$, *J* = 12.6); 3.83 (s, 3 H, OMe); 3.72 (s, 3 H, OMe); 2.92 (d, 1 H, $SCH_2$, *J* = 12.6); 1.71 (s, 3 H, Me) | 452 $[M]^+$ (9), 436 (5), 272 (100), 271 (19), 204 (64), 176 (13) |
| **4f** | 9.01 (br.s, 1 H, NH); 7.75 (d, 2 H, $C_6H_4CF_3$, *J* = 8.2); 7.61 (d, 2 H, $C_6H_4CF_3$, *J* = 8.2); 7.51—7.27 (m, 4 H, $C_6H_4S$); 6.68 (s, 2 H, $C_6H_2Me_3$); 5.31 (d, 1 H, $NCH_2Ar$, *J* = 17.4); 4.89 (d, 1 H, $NCH_2Ar$, *J* = 17.4); 4.38 (d, 1 H, $SCH_2$, *J* = 13.4); 3.01 (d, 1 H, $SCH_2$, *J* = 13.4); 2.18 (s, 3 H, MeAr); 1.69 (s, 3 H, Me); 1.67 (s, 6 H, $Me_2Ar$) | 512 $[M]^+$ (11), 493 (8), 350 (100), 351 (21), 159 (81), 137 (5) |
| **4g** | 9.05 (br.s, 1 H, NH); 7.53—7.26 (m, 4 H, $C_6H_4S$); 6.73 (s, 2 H, $C_6H_2Me_3$); 4.38 (d, 1 H, $SCH_2$, *J* = 13.9); 3.23 (d, 1 H, $SCH_2$, *J* = 13.9); 2.78—2.73 (m, 1 H, $C_3H_5$); 2.15 (s, 3 H, MeAr); 1.96 (s, 3 H, Me); 1.71 (s, 6 H, $Me_2Ar$); 1.03—0.91 (m, 4 H, $C_3H_5$) | 394 $[M]^+$ (4), 232 (100), 231(20), 218 (11), 204 (12) |
| **4h** | 8.67 (s, 1 H, Py); 8.45 (d, 1 H, Py, *J* = 2.7); 7.96 (d, 1 H, Py, *J* = 6.6); 7.46 (dd, 1 H, Py, *J* = 6.5, *J* = 2.7); 7.37—7.28 (m, 4 H, $C_6H_4S$); 6.42 (br.s, 1 H, NH); 5.39 (d, 1 H, $NCH_2Py$, *J* = 16.2); 4.66 (d, 1 H, $NCH_2Py$, *J* = 16.2); 4.13 (d, 1 H, $SCH_2$, *J* = 12.9); 2.52 (d, 1 H, $SCH_2$, *J* = 12.9); 1.90 (br.s, 3 H, Ad); 1.59 (br.s, 12 H, Ad); 1.47 (s, 3 H, Me) | 461 $[M]^+$ (1), 283 (100), 284 (19), 135 (12), 92 (68) |
| **4i** | 7.50—7.25 (m, 4 H, $C_6H_4S$); 6.69 (br.s, 1 H, NH); 4.27 (d, 1 H, $SCH_2$, *J* = 12.8); 2.92—2.89 (m, 1 H, $C_3H_5$); 2.75 (d, 1 H, $SCH_2$, *J* = 12.8); 1.91 (br.s, 3 H, Ad); 1.67 (br.s, 6 H, Ad); 1.58 (s, 3 H, Me); 1.54 (br.s, 6 H, Ad); 0.91—0.84 (m, 4 H, $C_3H_5$) | 410 $[M]^+$ (2), 232 (88), 231 (20), 190 (13), 135 (100) |
| **4j** | 9.40 (br.s, 1 H, NH); 7.36—7.12 (m, 9 H, Ph and $C_6H_4S$); 6.82 (d, 2 H, $C_6H_4N$, *J* = 9.1); 6.69 (d, 2 H, $C_6H_4N$, *J* = 9.1); 5.91 (d, 1 H, $NCH_2Ph$, *J* = 16.1); 4.38 (d, 1 H, $NCH_2Ph$, *J* = 16.1); 4.13 (d, 1 H, $SCH_2$, *J* = 12.3); 3.72 (t, 4 H, $O(CH_2)_2$, *J* = 4.6); 3.02 (t, 4 H, $N(CH_2)_2$, *J* = 4.7); 2.28 (d, 1 H, $SCH_2$, *J* = 12.3); 1.61 (s, 3 H, Me) | 487 $[M]^+$ (7), 443 (5), 282 (86), 268 (56), 240 (19), 91 (100) |
| **4k** | 9.37 (br.s, 1 H, NH); 7.83 (d, 2 H, $C_6H_4CF_3$, *J* = 7.8); 7.62 (d, 2 H, $C_6H_4CF_3$, *J* = 7.8); 7.35—7.16 (m, 4 H, $C_6H_4S$); 6.83 (d, 2 H, $C_6H_4N$, *J* = 8.9); 6.69 (d, 2 H, $C_6H_4N$, *J* = 8.9); 5.85 (d, 1 H, $NCH_2Ar$, *J* = 16.4); 4.56 (d, 1 H, $NCH_2Ph$, *J* = 16.4); 4.21 (d, 1 H, $SCH_2$, *J* = 12.5); 3.72 (t, 4 H, $O(CH_2)_2$, *J* = 4.7); 3.02 (t, 4 H, $N(CH_2)_2$, *J* = 4.7); 2.40 (d, 1 H, $SCH_2$, *J* = 12.6); 1.60 (s, 3 H, Me) | 555 $[M]^+$ (9), 540 (6), 350 (100), 191 (46), 177 (18), 159 (60) |
| **4l** | 9.43 (br.s, 1 H, NH); 7.50 (d, 2 H, $C_6H_4OMe$, *J* = 8.5); 7.32—7.13 (4 H, m, 4CH, $C_6H_4S$); 6.86 (d, 2 H, $C_6H_4OMe$, *J* = 8.5); 6.82 (d, 2 H, $C_6H_4N$, *J* = 9.2); 6.69 (d, 2 H, $C_6H_4N$, *J* = 8.9); 5.87 (d, 1 H, $NCH_2Ar$, *J* = 15.9); 4.28 (d, 1 H, $NCH_2Ar$, *J* = 15.9); 4.10 (d, 1 H, $SCH_2$, *J* = 12.2); 3.78 (s, 3 H, $OCH_3$); 3.72 (t, 4 H, $O(CH_2)_2$, *J* = 4.6); 3.02 (t, 4 H, $N(CH_2)_2$, *J* = 4.6); 2.25 (d, 1 H, $SCH_2$, *J* = 12.2); 1.61 (s, 3 H, Me) | 517 $[M]^+$ (10), 473 (7), 312 (100), 284 (65), 270 (16), 121 (72), 107 (19) |

replacement of chloroacetone by bromoacetophenone results in a sharp decrease in the degree of conversion of the reactants at the second stage, which precluded isolation of the target product. The replacement of methanol by another, less polar solvent also has an adverse effect. These analogies would enable the proper choice of the starting compounds and the reaction conditions in the further development of this method for the preparation of 1,4-benzothiazepin-5-one derivatives.

Thus, we proposed an original one-pot method for the synthesis of 1,4-benzothiazepin-5-one derivatives based on a combination of S-alkylation and four-component Ugi condensation. The scope and limitations and the routes for further development of this method were elucidated. The method can provide an alternative to the solid-state syntheses of combinatorial libraries of 1,4-benzothiazepin-5-ones.

## Experimental

The reactions were monitored and the product purity was checked by TLC on Silufol-254 and Sorbfil-254 plates in chloroform and chloroform—ethanol solvent systems (9 : 1; 15 : 1; 20 : 1). The $^1$H NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 MHz) in DMSO-$d_6$ or in a DMSO-$d_6$—$CCl_4$ system with $Me_4Si$ as the internal standard. Mass spectra were recorded on a Varian MAT 311A instrument at an accelerating voltage of 3 kV and an ionization energy of 70 eV with direct sample injection into the ion source. The melting points were not corrected.

***N*-Benzyl-*N*-(1-*tert*-butylcarbamoyl-1-methylethyl)-2-mercaptobenzamide (3).** Acetone (0.2 mmol), *tert*-butyl isocyanide (0.2 mmol), and benzylamine (0.2 mmol) were added to a solution of thiosalicylic acid (0.2 mmol) in methanol (0.25 mL). After keeping at ~20 °C for 24 h, the reaction mixture was diluted with water and extracted with chloroform (2 mL), and the organic layer was separated and applied onto silica gel. The product was purified by flash chromatography (silica gel 40/5μ, elution with a 9 : 1 chloroform—ethanol mixture). Yield 43 mg (56%), m.p. 127—128 °C. $^1$H NMR (DMSO-$d_6$), δ: 8.85 (br.s, 1 H, NH); 7.40—7.12 (m, 9 H, Ph and $C_6H_4S$); 5.66, 4.46 (both d, each 1 H, $NCH_2Ph$, $J$ = 15.8 Hz); 3.83 (s, 1 H, HS); 1.41 (s, 6 H, 2 Me); 1.18 (s, 9 H, $Bu^t$). Found (%): C, 68.54; H, 7.27; N, 7.35. $C_{22}H_{28}N_2O_2S$. Calculated (%): C, 68.75; H, 7.29; N, 7.29.

**1,4-Benzothiazepin-5-ones 4a—l (general procedure).** Potassium carbonate (0.22 mmol) and chloroacetone (0.22 mmol) were added to a solution of thiosalicylic acid (0.22 mmol) in methanol (0.25 mL). The reaction mixture was stirred for 1 h at ~20 °C and then isocyanide (0.2 mmol) and primary amine (0.2 mmol) were added. After keeping at ~20 °C for 24 h, the reaction mixture was diluted with water and extracted with chloroform (2 mL) and the organic layer was separated and

**Table 2.** Yields, melting points, and elemental analysis data for 1,4-benzothiazepin-5-ones **4a—l**

| Compound | Yield (%) | M.p./°C | Found / Calculated (%) | | | Molecular formula |
|---|---|---|---|---|---|---|
| | | | C | H | N | |
| **4a** | 51 | 148—149 | 70.05 / 70.11 | 6.15 / 6.07 | 9.40 / 9.44 | $C_{26}H_{27}N_3O_2S$ |
| **4b** | 55 | 203—204 | 66.38 / 66.21 | 5.71 / 5.75 | 9.75 / 9.66 | $C_{24}H_{25}N_3O_3S$ |
| **4c** | 84 | 180—181 | 67.98 / 68.21 | 6.17 / 6.11 | 8.80 / 8.84 | $C_{27}H_{29}N_3O_3S$ |
| **4d** | 52 | 173—174 | 64.95 / 64.79 | 5.45 / 5.40 | 9.18 / 9.07 | $C_{25}H_{25}N_3O_4S$ |
| **4e** | 64 | 145—146 | 63.66 / 63.72 | 5.39 / 5.31 | 6.38 / 6.19 | $C_{24}H_{24}N_2O_5S$ |
| **4f** | 50 | 163—164 | 61.12 / 60.94 | 5.25 / 5.27 | 5.56 / 5.47 | $C_{26}H_{27}F_3N_2O_2S$ |
| **4g** | 50 | 237—238 | 69.93 / 70.05 | 6.66 / 6.60 | 7.00 / 7.11 | $C_{23}H_{26}N_2O_2S$ |
| **4h** | 36 | 125—126 | 70.34 / 70.28 | 6.68 / 6.72 | 9.03 / 9.11 | $C_{27}H_{31}N_3O_2S$ |
| **4i** | 39 | 105—106 | 69.78 / 70.24 | 7.29 / 7.31 | 6.72 / 6.83 | $C_{24}H_{30}N_2O_2S$ |
| **4j** | 71 | 225—226 | 68.81 / 69.00 | 5.89 / 5.95 | 8.55 / 8.62 | $C_{28}H_{29}N_3O_3S$ |
| **4k** | 91 | 147—148 | 62.67 / 62.70 | 5.13 / 5.05 | 7.64 / 7.57 | $C_{29}H_{28}F_3N_3O_3S$ |
| **4l** | 74 | 152—153 | 67.45 / 67.31 | 6.08 / 6.00 | 8.04 / 8.12 | $C_{29}H_{31}N_3O_4S$ |

applied onto silica gel. The product was purified by flash chromatography (silica gel 40/5μ, elution with a 9 : 1 chloroform—ethanol mixture). The $^1$H NMR and mass spectra of the obtained compounds are listed in Table 1 and the yields, melting points, and elemental analysis data are in Table 2.

## References


1. R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471.
2. L. Weber, K. Illgen, and M. Almstetter, *Synlett*, 1999, 366.
3. I. Ugi and A. Doemling, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168.
4. M. Mironov, M. Kleban, V. Berseneva, V. Mokrushin, and V. Bakulev, *Abstract Book. First Symposium of the European Society for Combinatorial Sciences,* Budapest, 2001, L44.
5. T. Godfraind, R. Miller, and M. Wibo, *Parmacol. Rev.*, 1986, **38**, 21.
6. J. Slade, J. L. Stanton, D. Ben-David, and G. C. Mazzenga, *J. Med. Chem.*, 1985, **28**, 1517.
7. A. Nefzi, N. A. Ong, M. A. Giulianotti, J. M. Ostresh, and R. A. Houghten, *Tetrahedron Lett.*, 1999, **40**, 4939.
8. M. K. Schwarz, D. Tumelty, and M. A. Gallop, *J. Org. Chem.*, 1999, **64**, 2219.
9. N. K. Terrett, *Combinatorial Chemistry*, Oxford University Press, 1998, 186 p.
10. A. Doemling, K.-Z. Chi, and M. Barrere, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2871.
11. K. M. Short and A. M. M. Mjalli, *Tetrahedron Lett.*, 1997, **38**, 359; J. Zhang, A. Jacobson, J. R. Rusche, and W. Herlihy, *J. Org. Chem.*, 1999, **64**, 1074; S. Marcaccini, R. Pepino, T. Torroba, D. Miguel, and M. Garcia-Valverde, *Tetrahedron Lett.*, 2002, **43**, 8591.


*Received December 29, 2003*