Preparation of 2-Amino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones

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2-Amino substituted 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **11a-e** were prepared by the reaction of 2-bromo-5-amino-1,3,4-thiadiazole (**1b**) and diketene (**8**), subsequent cyclocondensation (**9b** → **3b**) and displacement of the bromo substituents by the reaction with primary or secondary amines (**3b** → **11a-e**). The hydrogen atom 6-H in the heterobicycle **3b** is replaced by a Cl or Br atom in the transformation of **3b** → **14a,b**. The 2-bromo-6-chloro compound **14a** reacts chemoselectively in the 2-position with dimethylamine (**14a** → **15**). The structure elucidations are based on one- and two-dimensional NMR techniques including a heteronuclear NOE measurement.

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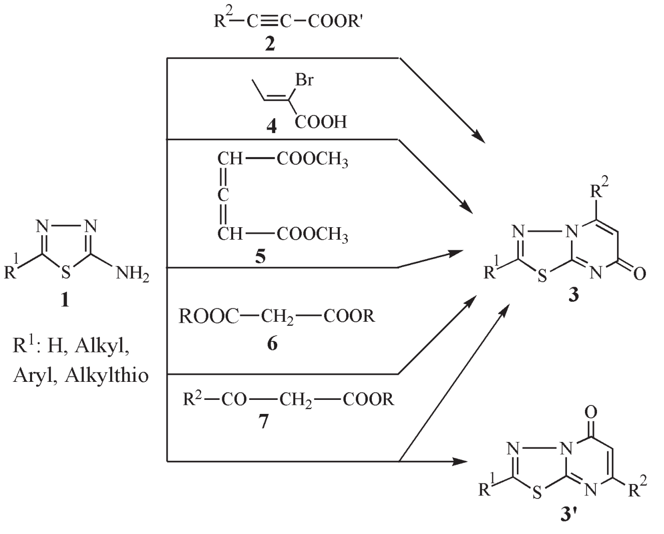
Introduction.

1,3,4-Thiadiazolo[3,2-*a*]pyrimidines have as pseudopurines [1] interesting biological and pharmacological properties [1-6]. A substantial amount of synthetic effort has been made for the preparation of 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**3**) (Scheme 1). This class of compounds can be obtained by condensation and subsequent cyclization reactions of 2-amino-1,3,4-thiadiazoles (**1**) with propiolates (**2**, R^2 = H) [1,7,8] or acetylene dicarboxylates (**2**, R^2 = COOR) [8]. Instead of **2**, masked alkynes like 2-bromocrotonic acid (**4**) can be used: **1** + **4** → **3** ($R^2 = CH_3$) [9,10]. Moreover, allene-1,3-dicarboxylate (**5**) furnishes **3** ($R^2 = CH_2\text{-}COOCH_3$) [11]. In contrast to malonic diesters (**6**), which yield the enol **3** (R^2 = OH) [9], *β*-keto esters (**7**) react with **1** to a give mixture of the isomers **3** and **3'**. The ratio **3**:**3'** depends strongly on the substituents R^2 and on the reaction conditions [12]. There are examples for which only one isomer **3** or **3'** was reported [7,13,14,15,16]. The yields of the procedures described for **3** in Scheme 1 are often very low.

Scheme 1

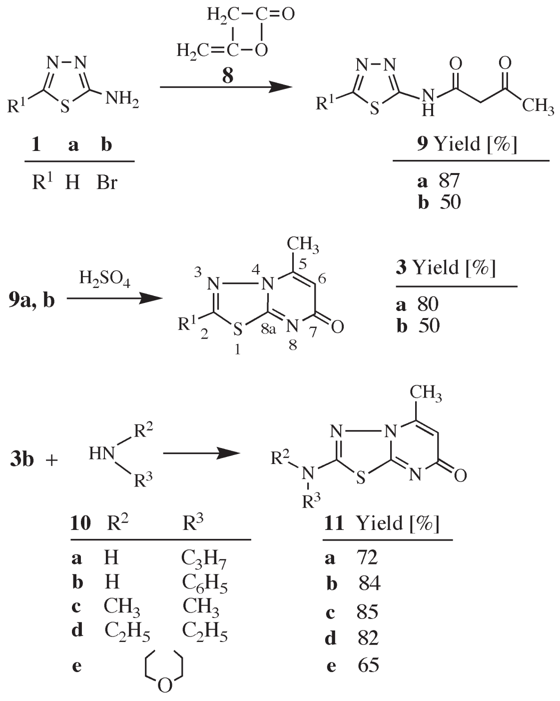


Additionally, the reactivity of **1** and *α*-cyano- [17] or *β*-aminocarbonyl compounds [18] were studied, but these processes turned out to be much more complicated. These results stimulated us to study a different approach to prepare compounds **3**, which moreover should enable the introduction of amino groups R^1, because we expect particularly promising biological properties for these compounds [13].

Results and Discussion.

The reaction of 2-amino-1,3,4-thiadiazoles (**1a**,**b**) with diketene (**8**) yielded selectively **3a**,**b** (Scheme 2). Due to the amino-imino tautomerism of **1**, the acylation could take place on the exocyclic nitrogen atom or on N-3, but in

Scheme 2



1	**a**	**b**
R^1	H	Br

9	Yield [%]
a	87
b	50

3	Yield [%]
a	80
b	50

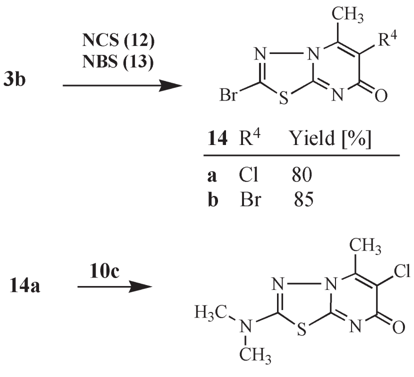
10	R^2	R^3
a	H	C_3H_7
b	H	C_6H_5
c	CH_3	CH_3
d	C_2H_5	C_2H_5
e	(morpholine ring)	

11	Yield [%]
a	72
b	84
c	85
d	82
e	65

contrast to the literature [14], we found only attack on the the amino group. The subsequent cyclocondensation with concentrated sulfuric acid led selectively to **3a**,**b**. A 1,3-acyl rearrangement of **9** [12] could not be observed. Consequently, the crude reaction product did not show any hints for the isomer **3'** (R^1 = H, R^2 = CH_3) in the ^1H and ^{13}C NMR spectra. The detection limit was below 3 %. Compound **3b** reacted with the primary amines **10a**,**b** and the secondary amines **10c**,**d**,**e** to the corresponding 2-amino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **11a-e** [19].

Chlorination of **3b** with *N*-chlorosuccinimide (NCS) (**12**) and bromination with NBS (**13**) gave the derivatives **14a** and **14b**, respectively (Scheme 3). The reagents **12** and **13**, dissolved in acetic acid, did not attack the 5-CH_3 group. Finally **14a** was transformed to **15** by the reaction with dimethylamine (**10c**); the 2-bromo substituent reacts chemoselectively. The behavior of **14b** is similar but less uniform.

Scheme 3



14	R^4	Yield [%]
a	Cl	80
b	Br	85

15 (50%)

The structure elucidation of **3**, **11**, **14** and **15** was based on ^1H and ^{13}C NMR measurements including two-dimensional techniques (HMBC) and the recording of heteronuclear Overhauser effects. Figure 1a shows the NOE difference spectrum of **3b**, which was obtained by irradiation into the signal of 6-H (δ = 6.07). The neighbor carbon atoms C-5 and C-7 exhibit high increases of their signal intensities. C-5 (δ = 147.5) gives a broad signal because of the remaining coupling, whereas C-7 (δ = 166.1) gives a slim signal. Figure 1b depicts the 2D measurement of **3b**, which permits the correlation of the other carbon atoms of the bicyclic scaffold as well. The 5-CH_3 group [δ (^1H) = 2.48] provokes cross peaks at δ (^{13}C) = 109.2 and 147.5 ppm, which correspond to C-6 and C-5, respectively. According to a ^4J coupling, a smaller cross peak can be seen for C-8a (δ = 163.7). The proton 6-H furnishes cross peaks at 109.2 (^1J) for C-6, 147.5 (^2J) for C-5 and 166.1 (^2J) for C-7. Based on these assignments, the ^{13}C chemical shifts of the other 5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones were determined (Table 1).

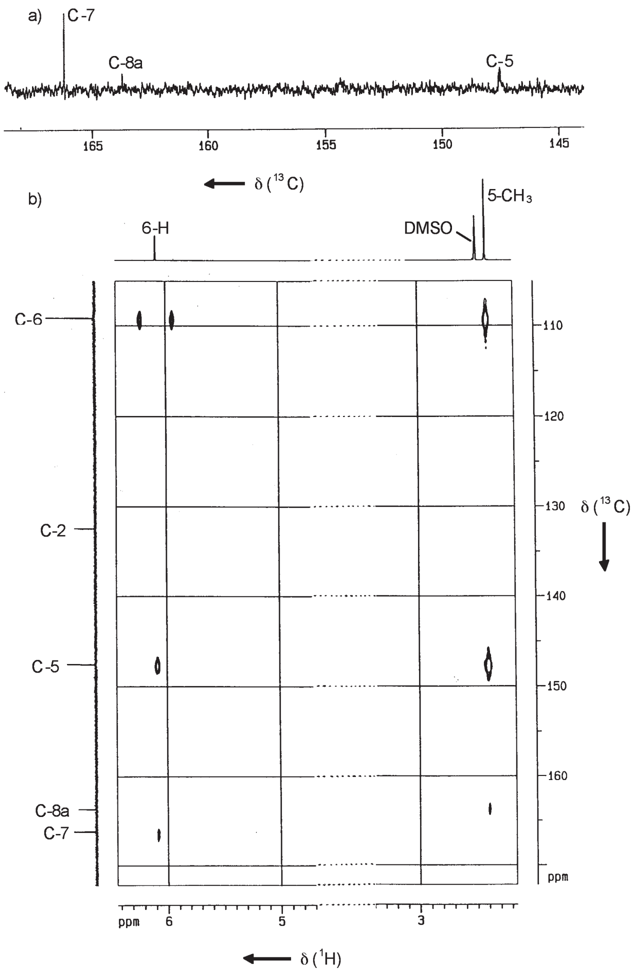


Figure 1. NMR study of compound **3b**: a) Section of the ^{13}C NOE difference spectrum obtained in CD_3SOCD_3 by irradiation into the signal of 6-H; b) Section of the ^1H,^{13}C shift correlation (measurement in CD_3SOCD_3 at 600 MHz).

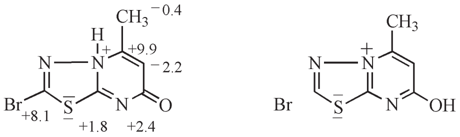
All obtained heterobicycles were highly soluble in polar solvents like methanol or DMSO, but less soluble in chloroform. Their basic character is important for the solution in trifluoroacetic acid CF_3COOH/CF_3COOD. The changes of the ^{13}C chemical shifts, shown in Scheme 4, make a protonation/deuteration on *N*-3 and/or *N*-4 (**3b** → **16**) more likely than the possible aromatic structure **17** which would be obtained by an *O*-protonation (Scheme 4).

Table 1

^{13}C NMR Data of 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **3**, **11**, **14** and **15**.

Compound	Solvent	C-2	C-5	C-6	C-7	C-8a	5-CH_3	Substituents
3a	CD_3SOCD_3	146.7	147.7	109.2	167.0	162.7	17.5	—
3b	$CDCl_3$	131.5	147.1	110.4	166.7	163.4	18.1	—
	CD_3SOCD_3	132.5	147.5	109.2	166.1	163.7	17.4	—
11a	CD_3OD	158.4	151.1	109.3	171.4	162.3	18.4	11.7 (CH_3) 23.0 (CH_2) 46.9 (NCH_2)
11b	CD_3SOCD_3	151.5	147.3	108.4	166.8	159.4	17.8	139.3 (C_i) 118.0 (*o*-C) 129.4 (*m*-C) 123.2 (*p*-C)
11c	CD_3OD	160.8	151.0	109.6	171.1	162.6	18.4	40.2 (CH_3)
11d	CD_3OD	159.2	150.9	109.6	171.2	162.3	18.4	47.0 (CH_2) 12.7 (CH_3)
11e	$CDCl_3$	158.9	147.7	109.5	168.0	160.1	18.3	48.1 (CH_2N) 65.7 (CH_2O)
14a	CD_3SOCD_3	133.8	145.3	118.0	162.4	161.2	16.3	—
14b	CD_3SOCD_3	133.6	146.7	110.7	162.8	161.5	19.1	—
15	CD_3OD	160.4	147.8	119.0	165.5	161.2	16.7	40.2 (CH_3)

Scheme 4



16 CF_3COO^- **17**

Conclusion.

The reaction of 2-amino-5-bromo-1,3,4-thiadiazole (**1b**) with diketene (**8**) yielded *N*-(5-bromo-1,3,4-thiadiazol-2-yl)acetoacetamide (**9b**), which could be cyclized to 2-bromo-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**3b**). Primary and secondary amines permitted the replacement of the 2-bromo substituents by the corresponding amino groups (**3b** → **11a-e**). Chloro and bromo substituents could be introduced at C-6 of **3b** by the reaction with NCS and NBS, respectively. Finally a chemoselective exchange of the bromo substituent in **14a** by a dimethylamino group was possible (**14a** → **15**). Thus, a series of amino-substituted 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **11a-e** and **15** was obtained, for which interesting biological and/or pharmacological properties are expected.

EXPERIMENTAL

Melting points were determined on a Stuart Scientific SMP/3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with Bruker AM 400, AMX 400 and Avance 600 instruments. Mass spectra were obtained on a Finnigan MAT 95 spectrometer (FD technique) and a Micromass QTOF ULTIMA 3 (ESI technique). Elemental analyses were performed in the micro-analytical laboratory of the department.

2-Amino-1,3,4-thiadiazole (**1a**) [9] and 2-amino-5-bromo-1,3,4-thiadiazole (**1b**) [20] were generated according to the literature.

General Procedure for the Reaction of **1** and Diketene (**8**).

Diketene (**2**) [1.68 g, 20.0 mmol] was slowly added to a boiling suspension of 10.0 mmol **1a,b** in 200 mL benzene. The vigorously stirred mixture was monitored using TLC (SiO_2, DMSO) until the reaction is complete. The concentrated organic phase was stored over night at 6 °C and the precipitated product **9a** recrystallized from methanol; the crude **9b** was washed with 5 mL benzene, dissolved in 200 mL methanol and treated with activated charcoal. The filtered solution was evaporated and the residue recrystallized from ethanol/water (4:1).

N-(1,3,4-Thiadiazol-2-yl)acetoacetamide (**9a**).

The obtained colorless crystals (1.61 g, 87 %), mp 179 °C, correspond to an authentic sample [13].

N-(5-Bromo-1,3,4-thiadiazol-2-yl)acetoacetamide (**9b**).

Colorless crystals (1.32 g, 50 %) were obtained which melted at 174 °C. ^{1}H NMR (CD_3SOCD_3): δ 2.19 (s, 3 H, CH_3), 3.77 (s, 2 H, CH_2), 12.94 (br. s, 1 H, NH); ^{13}C NMR (CD_3SOCD_3): δ 30.4 (CH_3), 50.6 (CH_2), 134.6 (C-5), 160.7 (C-2), 166.3 (CONH), 201.8 (CO); FD MS: *m/z* 263 (90 %) / 265 (100 %) [$M^{+\bullet}$, Br isotope pattern].

Anal. Calcd. for $C_6H_6BrN_3O_2S$ (264.1): C, 27.29; H, 2.29; N, 15.91. Found: C, 27.30; H, 2.28; N, 15.89.

General Procedure for the Cyclocondensation Reaction **9** → **3**.

To 20 mL concentrated H_2SO_4, 10.0 mmol **8a,b** were slowly added under stirring. The solution was kept at 60 – 65 °C for about 15 h, cooled to -5 °C, and poured on 200 g crushed ice. After neutralization with saturated Na_2CO_3, the water phase was extracted with $CHCl_3$ (3 x 60 mL). Evaporation of the $CHCl_3$ gave a solid residue which was recrystallized from methanol.

5-Methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**3a**).

The obtained colorless crystals (1.34 g, 80 %), mp 195 °C correspond to an authentic sample [13a].

2-Bromo-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**3b**).

This compound was obtained in 80 % yield (2.09 g), mp 181 °C. ^1H NMR ($CDCl_3$): δ 2.48 (s, 3 H, CH_3), 6.09 (s, 1 H, 6-H); FD MS: *m/z* 245 (92 %), 247 (100 %) [$M^{+\bullet}$, Br isotope pattern].

Anal. Calcd. for $C_6H_4BrN_3OS$ (246.1): C, 29.28; H, 1.61; N, 17.08; S, 13.03. Found: C, 29.23; H, 1.70; N, 17.23; S, 13.12.

General Procedure for the Preparation of the 2-Amino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**11a – e**).

To 246 mg (1.0 mmol) **3b** in 5 – 7 mL ethanol, 4.0 – 8.0 mmol [21] of amine **10a-e** was added. After 1 – 4 h refluxing (monitored by TLC), the volatile parts were evaporated, 10 mL H_2O was added and the product extracted with 3 x 20 mL $CHCl_3$. Further purification was achieved by recrystallization from the solvent described for each compound.

2-Propylamino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**11a**).

Instead of ethanol, methanol was used. Recrystallization from methanol yielded 162 mg (72 %) crystals, mp 222 °C. ^1H NMR (CD_3OD): δ 1.04 (t, 3 H, CH_3), 1.71 (m, 2 H, CH_2), 2.52 (s, 3 H, 5-CH_3), 3.35 (t, 2 H, NCH_2), 6.18 (s, 1 H, 6-H) [22]; FD MS: *m/z* 224 (100 %) [$M^{+\bullet}$]; HR MS (ESI): Calcd. for $[C_9H_{13}N_4OS]^+$: 225.0863. Found 225.0805.

2-Phenylamino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**11b**).

Recrystallization from DMSO yielded 216 mg (84 %), mp 295 °C. ^1H NMR (CD_3SOCD_3): δ 2.48 (s, 3 H, CH_3), 6.01 (s, 1 H, 6-H), 7.07 (m, 1 H, *p*-H), 7.37 (m, 2 H, *m*-H), 7.51 (m, 2 H, *o*-H), 10.60 (br. s, 1 H, NH); FD MS: *m/z* 258 (100 %) [$M^{+\bullet}$].

Anal. Calcd. for $C_{12}H_9N_4OS$ (257.3): C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.82; H, 3.94; N, 21.50; S, 12.31.

2-Dimethylamino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**11c**).

Recrystallization from 1,4-dioxane yielded 179 mg (85 %), mp 202 °C. ^1H NMR (CD_3OD): δ 2.53 (s, 3 H, 5-CH_3), 3.16 (s, 6 H, $N(CH_3)_2$), 6.20 (s, 1 H, 6-H); FD MS: *m/z* 210 (100 %) [$M^{+\bullet}$].

Anal. Calcd. for $C_8H_{10}N_4OS$ (210.3): C, 45.70; H, 4.79; N, 26.65; S, 15.25 Found: C, 45.87; H, 4.67; N, 26.61; S, 15.24.

2-Diethylamino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**11d**).

Recrystallization from ethyl acetate/petroleum (1:1) yielded 195 mg (82 %), mp 113 °C. ^1H NMR (CD_3OD): δ 1.32 (t, 6 H, CH_3), 2.54 (s, 1 H, 5-CH_3), 3.57 (q, 4 H, NCH_2), 6.22 (s, 1 H, 6-H); FD MS: *m/z* 238 [$M^{+\bullet}$].

Anal. Calcd. for $C_{10}H_{14}N_4OS$ (238.3): C, 50.40; H, 5.52; N, 23.51; S, 13.45. Found: C, 50.69; H, 5.80; N, 23.80; S, 13.53.

5-Methyl-2-morpholino-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**11e**).

This compound was obtained in 65 % yield (165 mg), mp 227 °C ($CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.37 (s, 1 H, CH_3), 3.41 (m, 4 H, NCH_2), 3.76 (m, 4 H, OCH_2), 6.10 (s, 1 H, 6-H); FD MS: *m/z* 252 (100 %) [$M^{+\bullet}$]; HR MS (ESI): Calc. for $[C_{10}H_{13}N_4O_2S]^+$: 253.0759; found: 253.0754.

2-Bromo-6-chloro-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**14a**).

To 3 mL glacial acetic acid, 492 mg (2.0 mmol) **3b** and 534 mg (4.0 mmol) *N*-chlorosuccinimide (**12**) were added. After 1 h stirring at 95 °C, 2 mL petroleum (bp 40 – 70 °C) was added. The precipitate formed at 6 °C was washed with H_2O and recrystallized from CH_3OH. Yield 449 mg (80 %), mp 215 °C. ^1H NMR (CD_3SOCD_3): δ 2.59 (s, 3 H, CH_3); FD MS: *m/z* 279 (70 %), 281 (100 %), 283 (16 %) [$M^{+\bullet}$, BrCl isotope pattern].

Anal. Calcd. for $C_6H_3BrClN_3OS$ (280.5): C, 25.69; H, 1.08; N, 14.98. Found: C, 25.47; H, 1.00; N, 15.13.

2,6-Dibromo-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**14b**).

To 2.4 mL glacial acetic acid, 246 mg (1.0 mmol) **3b** and 356 mg (2.0 mmol) NBS (**13**) were added. After 0.5 h stirring at 90 °C, 2.5 mL petroleum (bp 40 – 70 °C) was added. The precipitate formed at 6 °C was washed with H_2O and recrystallized from CH_3OH. Yield 276 mg (85 %), mp 217 °C. ^1H NMR (CD_3SOCD_3): δ 2.63 (s, 3 H, CH_3); FD MS: *m/z* 323 (46 %), 325 (100 %), 327 (44 %) [$M^{+\bullet}$, Br_2 isotope pattern].

Anal. Calcd. for $C_6H_3Br_2N_3OS$ (325.0): C, 22.18; H, 0.93; N, 12.93; S, 9.87. Found: C, 22.52; H, 0.94; N, 12.95; S, 9.93.

6-Chloro-2-dimethylamino-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-7-one (**15**).

The solution of 150 mg (0.53 mmol) **14a** in 5 mL 1,4-dioxane/methanol (1:1) was treated with 180 mg (4.0 mmol) **10c**. After stirring and refluxing, the volatile parts were removed, 4 mL H_2O was added to the residue and the mixture extracted with 9 x 40 mL $CHCl_3$. Recrystallization from CH_3OH yielded 65 mg (50 %) of **15**, mp 260 °C. ^1H NMR (CD_3OD): δ 2.73 (s, 3 H, CH_3), 3.18 (s, 6 H, $N(CH_3)_2$); FD MS: *m/z* 244 (100 %), 246 (44 %) [$M^{+\bullet}$, Cl isotope pattern]; HR MS (ESI): Calc. for $[C_8H_{10}{}^{35}ClN_4OS]^+$: 245.0270. Found: 245.0185.

Acknowledgements.

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REFERENCES AND NOTES

[1] F. Russo, A. Santagati and M. Santagati, *J. Heterocyclic Chem.*, **22**, 297 (1985) and references therein.

[2] B. W. Clare and C. T. Supuran, *Eur. J. Med. Chem. Chim. Ther.*, 859 (2000).

[3] B. H. Lee, M. F. Clothier, F. E. Dutton, G. A. Conder and S. S. Johnson, *Bioorg. Med. Chem. Lett.*, **8**, 3317 (1998).

[4] A. R. Katritzky, K. C. Caster, T. H. Maren, C. W. Conroy and A. Bar-Ilan, *J. Med. Chem.*, **30**, 2058 (1987).

[5] S. Herling (Grünenthal G.m.b.H.), *Ger. Offen.* 2712932 (1978); *Chem. Abstr.*, **90**, 38957p (1978).

[6] S. Herling (Grünenthal G.m.b.H.), *Ger. Offen.* 2755615 (1979); *Chem. Abstr.*, **91**, 91655k (1979).

[7] A. Shafiee and I. Lalezari, *J. Heterocyclic Chem.*, **12**, 675 (1975).

[8] M. Daneshtalab and K. Motamedi, *J. Heterocyclic Chem.*, **17**, 785 (1980).

[9] R. F. Lauer and G. Zenchoff, *J. Heterocyclic Chem.*, **13**, 291 (1976).

[10] Another masked propiol system for this purpose is represented by 2,3-dichloroacrylic acid: J. G. Kuderna, R. D. Skiles and K. Pilgram, *J. Org. Chem.*, **36**, 3506 (1971).

[11] G. J. Doad, D. I. Okor and F. Scheinmann, *J. Chem. Soc. Perkin Trans. 1*, 2993 (1988).

[12] G. Kornis, P. J. Marks and C. G. Chidester, *J. Org. Chem.*, **45**, 4860 (1980).

[13] T. Okabe, E. Taniguchi and K. Maekawa, [a] *J. Fac. Agric., Kyushu Univ.*, **17** 195 (1973); *Chem. Abstr.*, **79**, 32002 (1973); [b] *Agric. Biol. Chem.*, **37**, 1197 (1973); [c] *Bull. Chem. Soc. Jpn.*, **47**, 2813 (1974); [d] *J. Fac. Agric., Kyushu Univ.*, **19**, 91 (1975).

[14] H. Paul and A. Sitte, *Monatsh. Chem.*, **102**, 550 (1971).

[15] T. Tsuji and K. Takenaka, *Bull. Chem. Soc. Jpn.*, **55**, 637 (1982).

[16] M. A. Kukaniev, *Dissertation*, Dushanbe, (1997).

[17] T. Tsuji, *J. Heterocyclic Chem.*, **28**, 489 (1991).

[18] J. Quiroga, B. Insuasti, P. Hernandez, R. Moreno, R. H. de Almeida and H. Meier, *Eur. J. Org. Chem.*, 1201 (1998).

[19] Ammonia yields a secondary amine with two thiadiazolopyrimidin-2-yl groups.

[20] S. A. Shams El-Dine and O. Clauder, *Acta Chem. Acad. Scient. Hung.*, **84**, 85 (1975).

[21] The reaction time is shortened by a high excess of amine; the yields of **11** are not significantly different when 8.0 instead of 4.0 mmol amine are used.

[22] At higher resolution the compounds **11a-e** exhibit in the ^{1}H NMR spectra an allylic coupling of $0.8 \le {}^4J \le 1.2$ Hz between 5-CH_3 and 6-H.