Ternary Condensation of Biginelli Thiones, Chloroacetic Acid, and Aldehydes as an Effective Approach towards Thiazolo[3,2-a] pyrimidines and 5-Arylidenethiazolidine-2,4-diones

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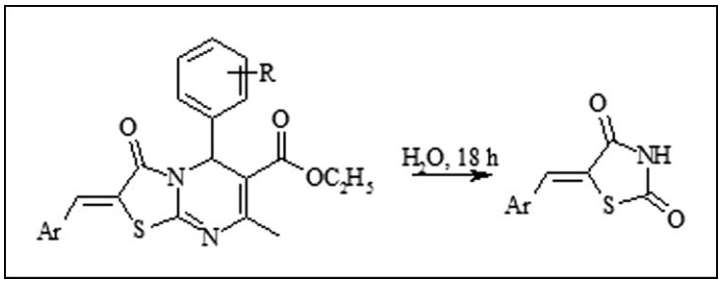
Received September 20, 2009
DOI 10.1002/jhet.323
Published online 4 March 2010 in Wiley InterScience (www.interscience.wiley.com).



At the process of ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates condensation with aryl aldehydes and chloroacetic acid the unexpected formation of 5-arylidenethiazolidine-2,4-diones was determined in high yields as the reaction time was increased to 20 h. The latter represent the products of destructive hydrolyzes of ethyl 2-benzylidene-7-methyl-3-oxo-5-aryl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates which have been proved by independent synthesis.

J. Heterocyclic Chem., **47**, 368 (2010).

INTRODUCTION

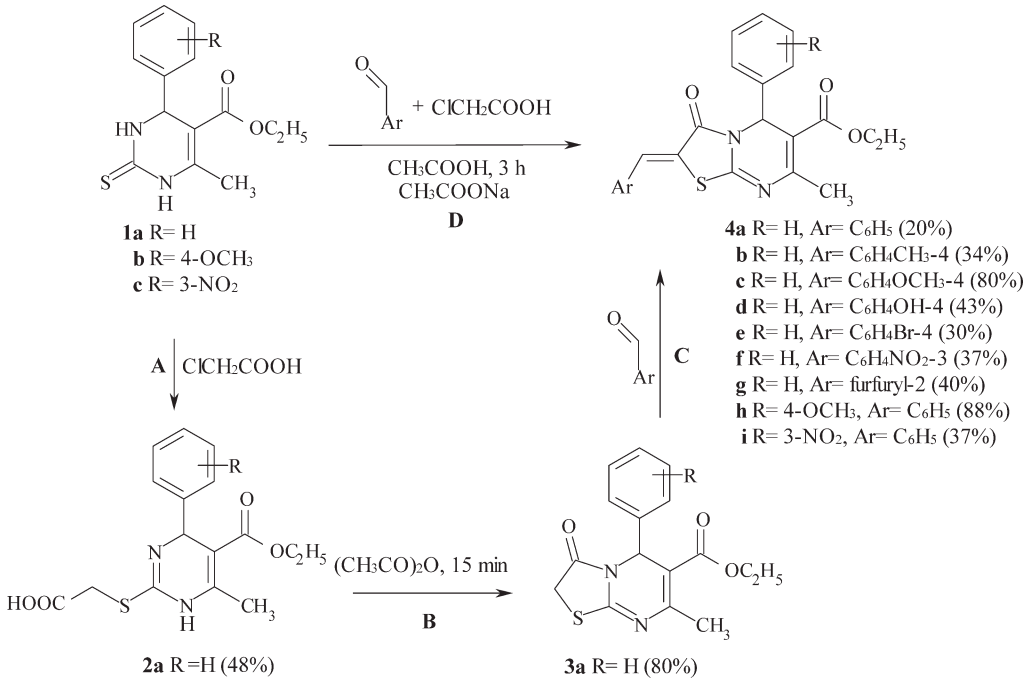
Multicomponent reactions (MCRs) have been widely used in organic and medicinal chemistry over the last years for producing a number of libraries for bioscreening [1]. A three-component condensation of aromatic aldehydes with ureas (thioureas) and β-ketoesters known as Biginelli reaction [2] takes an important place among MCRs. The reaction allows forming a dihydropyrimidine cycle where the nature of the subsistent in the basic structure can be widely modified. Dihydropyimidines (DHPMs) found their use as antimicrobial [3], antiviral [4], antiinflammatory [5], anticarcenogenic preparations [6], and calcium channel modulators [7]. The principle of Biginelli condensation is employed to construct complex heterocyclic scaffolds analogous to those isolated from Batzelladines A-B which have been found to be potent HIVgp-120-CD4 inhibitors [8]. To broaden the study on the range of biological activity of 2-thioxo-DHPM derivatives the library of substituted ethyl 5-aryl-3-oxo-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates (**4a–i**) have been synthesized [9].

A standard method of a multicomponent one-step condensation of substituted pyrimidine-2-thiones **1a** [9], **1b** [9], **1c** [2(b,f)], haloacetic acids, aryl(heteryl)aldehydes and surplus of anhydrous sodium acetate using glacial acetic acid as solvent has been employed. The formation of corresponding thiazolo[3,2-*a*]pyrimidine derivatives **4a–i** (**D**, Scheme 1) results in three consecutive stages which include alkylation leading to the compound **2a** (**A**, Scheme1) formation [2(c)], intramolecular heterocyclisation **3a** (**B**, Scheme 1) [9(c,h)], and condensation (**C**, Scheme 1) [9(a)] of primary DHPMs **1a–c**. Thus, a newly formed heterocyclic system **3a**, readily reacts with carbonyl compounds giving rise to substituted arylidene derivarives **4a–i**. The reaction time depends on the carbonyl reagent and lasts for 1–3 h. It is obvious that at the condensation of this type 7*H* isomer may be formed together with the 5*H* one (**4a–i**). Unambiguous formation of **4a–i** type ending products has been previously established with the extensive X-ray study [9(c)].

RESULTS AND DISCUSSION

Quite unexpectedly, as the reaction time (**D**, Scheme 1) was increased to 18–20 h, the final products, extracted from the reaction mixture, were identified as 5-arylidene-2,4-thiazolidinediones (**5a–g**, Scheme 2) [10]. Thus, thiazolo[3,2-*a*]pyrimidines **4a–i** represent

Scheme 1



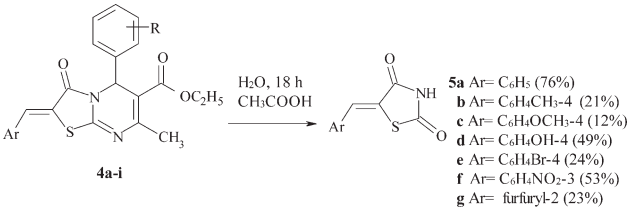
intermediate products for the synthesis of **5**-arylidene-2,4-thiazolidinediones (**5a–g**).

To determine the conditions when the destruction process takes place, a series of technical mixtures extracted from the mother liquor on different stages of the reaction time has been studied. A sample, taken in 30 min of reaction mixture reflux revealed the presence of the primary compound **1a** 27% and the intermediate product **4a** 72%. The destruction product **5a** was not determined on this reaction stage. Specimen, extracted in 3 h of reflux, revealed the presence of thiazolo[3,2-*a*]pyrimidine **4a** at the amount of 88% and 11% of 5-arylidene-thiazolidine-2,4-dione (**5a**). Sample, taken in 18 h of reaction mixture reflux contained both **5a** 76 and **4a** 20%, respectively. It should be noted that refluxing **4a** as a starting compound under the condensation conditions (glacial acetic acid, anhydrous sodium acetate, corresponding aromatic aldehyde), for 20 h did not reveal the presence of 5-arylidene thiazolidine-2,4-dione (**5a**). As water was added to the analogous reaction mixture to **4e**, the ratio of target products was **5e** 24, to **4e** 30%. 5-Arylidenethiazolidine-2,4-dione (**5a**) was formed in 55% yield when alkylated dihydropyrimidine-2-thione (**2a**) was used as a primary compound and cyclization took place under standard reaction duration and conditions. As analogous reaction conditions were followed excluding presence of water for **3a** as a primary compound the destruction process was not determined and reaction mixture contained 95% of thiazolo[3,2-*a*]pyrimidine **4a**. The exclusion of anhydrous sodium acetate from the reaction somewhat speeds up the destruction process and in 8 h of reaction time the ratio of **4a** to **5a** was 38 to 42%.

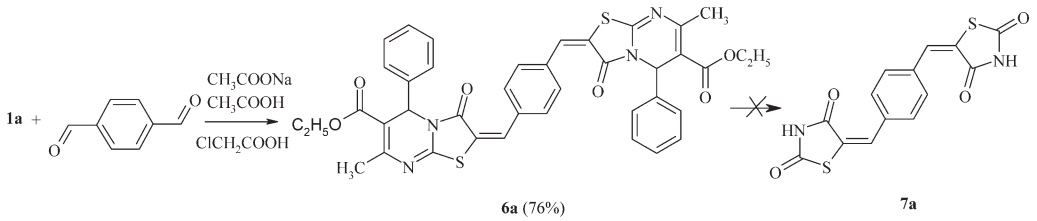
Thus, it may be concluded that the destruction process takes place due to slow hydrolyses of **4a–i** with water emitted during the condensation course. Therefore, the presence of anhydrous sodium acetate is obviously not enough to exclude the influence of water on the reaction course. As acetic anhydride surplus is added to the reaction mixture the process of destructive hydrolyses had not been determined either on the 3rd or on the 18th h of the reaction duration and the presence of formed thiazolo[3,2-*a*]pyrimidines (**4a**) was 97% and 98% respectively.

As terephthalic aldehyde was employed in ethyl thiazolo[3,2-*a*]pyrimidine-6-carboxylates synthesis, bis-thiazolo[3,2-*a*]pyrimidine of **6a** type (Scheme 3) has been obtained as a target product. It should be mentioned that possible destruction product (**7a**, Scheme 3) was not determined even under rigid reaction conditions such as

Scheme 2



Scheme 3



synthesis of **6a** in a sealed tube at 180°C for 12 h due to **6a** possessing low ability to dissolve in organic solvents.

The structure of compounds **5a–g** has been determined by NMR (^{1}H, ^{13}C), IR, elemental, LC/MS analyses. ^{1}H NMR spectra of compounds **5a–g** are characterized with the presence of the representative singlet at 6.0–6.1 ppm corresponding to the one of pyrimidine cycle at C4, and also with the singlet at 7.6–7.9 ppm relevant to the proton of methine group of the multiple bond C=CH-Ar. For **6a** corresponding signals are determined at 6.52 and 8.31 ppm at CF_3COOD.

^{13}C NMR spectroscopy was also applied to determine the structure of **5a** revealing eight signals. APT experiment determined the presence of four quaternary carbon atoms including two carbonyle and four protonated tertiary carbon atoms: δ = 167.65 (q), 167.09 (q), 132.85 (q), 131.61 (t), 130.20 (t), 129.83 (t), 129.10 (t), 123.36 (q) ppm. IR spectra of **5a–g** (KBr platelets) revealed broadened picks due to the intermolecular bonds of ÑH and C=O groups. The structure of **5a** has been unambiguously determined by the single crystal X-ray diffraction. The perspective view of the molecule **5a** and selected geometrical parameters are given in Figure 1. The molecule **5a** is almost planar (deviations of nonhydrogen atoms from the least-square plane do not exceed 0.069 Å). The N(1) atom has trigonal-planar bond configuration (sum of the bond angles 360.0°).

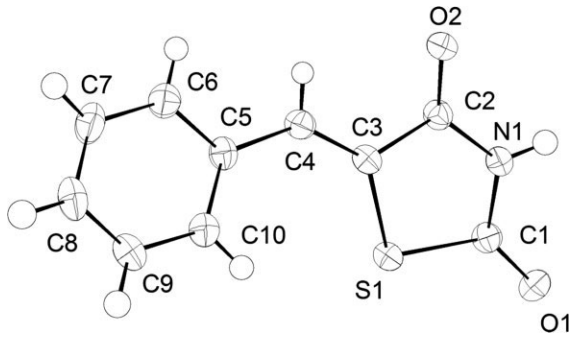


Figure 1. Perspective view and labeling scheme for the molecule **5a.** Selected bond lengths (Å) and angles (°): S(1)-C(1) 1.786(2), S(1)-C(3) 1.756(2), N(1)-C(1) 1.369(2), N(1)-C(2) 1.365(2), C(2)-C(3) 1.484(2), C(3)-C(4) 1.331(2); C(1)S(1)C(3) 91.68(8), C(1)N(1)C(2) 117.9(1).

Because of the n_N-$\pi_{C=O}$ conjugation both the N(1)-C(1) 1.369(2) Å and the N(1)-C(2) 1.365(2) Å bonds are significantly shortened in comparison with the standard value for the N(sp^2)-C(sp^2) single bonds of 1.43–1.45 Å [11,12]. In the solid state the molecules of **5a** are joined in the centrosymmetric dimers by the N(1)-H...O(2) (N...O 2.834(2), O...H 1.96(2) Å, NHO 169(23)° intermolecular hydrogen bonds.

CONCLUSIONS

The formation of 5-arylidene-2,4-thiazolidinediones has been determined during the synthesis of substituted ethyl 5-aryl-3-oxo-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates library. Therefore, it is strongly suggested to reconsider the traditional reaction conditions and to take special care on the exclusion of water influence on the reaction process (*e.g.* acetic anhydride should be employed at the reaction rather than waterfree sodium acetate). Otherwise, as the reaction time expanded for the period of 18 h and more, allowing the emitted water to hydrolyze the desired thiazolo[3,2-*a*]pyrimidines the formation of 5-arylidene-2,4-thiazolidinediones reaches up to 76%.

EXPERIMENTAL

All chemicals were obtained from commercial sources and used without further purification. Melting points (mp) were measured on an electrothermal capillary melting point apparatus and are uncorrected. IR spectra were recorded with a UR-20 spectrophotometer (KBr platelets). The NMR measurements were carried out on a Varian GEMINI 2000 spectrometer with ^{1}H and ^{13}C frequencies of 400.07 and 100.61 MHz, respectively at 293 K. ^{1}H NMR spectra were recorded with spectral width 8000 Hz and numbers of points 32,000; ^{13}C NMR spectra were recorded with spectral width 30,000 Hz and numbers of points 128,000. DMSO-d_6 and CF_3COOD were used as solvents and TMS as internal standard. HPLC-MS was carried out on a system consisting of an Agilent 1100 Series high-pressure liquid chromatograph equipped with a diode matrix and Agilent LC/MSD SL mass-selective detector. HPLC-MS parameters: column: Zorbax SB-C18, 1.8 μm, 4.6 × 30 mm^2; solvents: Me-CN-H_2O (95:5), 0.1% TFA; eluent flow: 3 mL s^{-1}; injected sample volume: 1 μL; UV detector: λ = 215, 254, 265 nm; ionization method: chemical ionization

under atmospheric pressure (APCI); ionization mode; simultaneous scanning of positive and negative ions in *m/z* range 100–650. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Crystallographic data of **5a** including atomic coordinates, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Camridge CB2 1EZ, UK, fax: +44 1223 336 033, or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 734605.

General procedures. ***4-Phenyl-5-carbethoxy-6-methylpyrimidine-2-mercaptoacetic acid (2a).*** A solution of **1a** 2.76 g (0.01 mole) and bromoacetic acid 1.5 g (0.011 mole) was refluxed in 15 mL acetic acid for 30 min. Then the mixture was taken to dryness *in vacuo*. The remained residue was neutralized with sodium carbonate solution to pH 5, filtered, washed with 100 mL of hot water. Recrystallized from EtOH. Compound **2a** was obtained as yellow solid in 68% yield. Mp and spectral data has appeared to be identical to those reported in literature [2(c)].

Ethyl 5-phenyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a]pyrimidine-6-carboxylate (3a). Compound **2a** 1.82 g, (0.005 mole) was dissolved in 5 mL acetic anhydride and refluxed for 15 min, and then allowed to cool. The precipitate formed was filtered off and recrystallized from *i*-PrOH. Compound **3a** was obtained as yellow solid in 80% yield. Mp and spectral data has appeared to be identical to those reported in literature [2(c),10(a,b)].

General procedure for the synthesis of ethyl 5-arylmethylene-3-oxo-7-methyl-2,3-dihydro-5H-thazolo[3,2-*a*]pyrimidine-6-carboxylates (4a–i). A mixture of **1a–c** (0.01 mole), anhydrous sodium acetate 1.0 g, (0.015 mole), chloroacetic acid 1.0 g, (0.011 mole), and the appropriate aldehyde (0.01 mole) was refluxed for 3 h in 10 mL of glacial AcOH. After cooling, the mixture was poured onto crushed ice. The precipitate formed **4a–i** was filtered off and recryatllized from *i*-PrOH.

Compounds (Yield) **4a** [9(c)] (20%), **4b** [9(c)] (34%), **4c** [9(c,g)] (80%), **4e** [9(f)] (30%), **4h** [9(e)] (88%), **4i** [9(c)] (37%) have been described in the literature.

Ethyl 5-phenyl-2-(4-hydroxyphenylmethylene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4d). Yellow solid, yield 43%, mp 192°C (*i*-PrOH); IR (KBr): ν 1545 (C=N), 1695 (C=O), 2990 (CH) 3430 (OH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.22 [s, 1 H, OH], 7.66 [s, 1H, HOC_6H_4CH], 7.39 [d, ^3J(H,H) = 8.8 Hz, 2 H, H2 H6 C_6H_4OH], 7.30 [m, 5 H, C_6H_5], 6.87 [d, ^3J(H,H) = 8.8 Hz, 2 H, H3 H5 C_6H_4OH], 6.03 [s, 1 H, C_6H_5CH], 4.05 [m, 2 H, CH_2CH_3], 2.40 [s, 3 H, $NCCH_3$], 1.16 [t, ^3J(H,H) = 8.0 Hz, 3 H, CH_2CH_3]; ms: *m/z* 419 (M^-). *Anal*. *C*alcd. for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66. Found: C, 64.39; H, 4.70; N, 6.73.

Ethyl 5-phenyl-2-(3-nitrophenylmethylene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4f). Yellow solid in 37% yield, mp 173°C (*i*-PrOH); IR (KBr): ν 1330, 1540 (NO_2), 1610 (C=N), 1690, 1730 (C=O) 2980 (CH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.39 [deg. s, 1 H, H2 $C_6H_4NO_2$], 8.25 [d, ^3J(H,H) = 8.0 Hz, 1 H, H6 $C_6H_4NO_2$], 7.96 [d, ^3J(H,H) = 7.6 Hz, 1 H, H4 $C_6H_4NO_2$], 7.90 [s, 1 H, $O_2NC_6H_4CH$], 7.78 [m. 1 H, H5 $C_6H_4NO_2$], 7.32 [m, 5 H, C_6H_5], 6.08 [s, 1 H, C_6H_5CH], 4.08 [m, 2 H, CH_2CH_3], 2.42 [s, 3 H, CH_3], 1.16 [t, ^3J(H,H) = 6.8 Hz, 3 H, CH_2CH_3]; ms: *m/z* 450 (M^+). *Anal*. Calcd. for $C_{23}H_{19}N_3O_5S$: C: 61.46; H, 4.26; N, 9,35. Found: C, 60.24; H, 4.19; N, 9.42.

Ethyl 5-phenyl-(2-furfuryl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4g). Grey solid in 40% yield, mp 149–150°C (*i*-PrOH); IR (KBr): ν 1600 (C=N), 1690 (C=O) 2960 (CH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.06 [deg. s, 1 H, 5-H fur], 7.61 [s, 1 H, furCH], 7.33 [m, 5 H, C_6H_5], 7.09 [deg. s, 1 H, 3-H fur], 6.74 [deg. s, 1 H, 4-H fur], 6.05 [s, 1 H, C_6H_5CH], 4.06 [m, 2 H, CH_2CH_3], 2.39 [s, 3 H, CH_3], 1.13 [t, ^3J(H,H) = 7.2 Hz, 3 H, CH_2CH_3]; *m/z* 395 (M^+). *Anal*. Calcd. for $C_{21}H_{18}N_2O_3S$: C, 63.95; H, 4.60; N, 7.10. Found: C, 62.69; H, 4.53; N, 7.18.

General procedure for the synthesis of substituted 5-arylidene-2,4-thiazolidinedione (5 a–g). A mixture of **1a–c** (0.01 mole), anhydrous sodium acetate 1.0 g (0.015 mole), chloroacetic acid 1.0 g (0.011 mole), and the appropriate aldehyde (0.01 mole) was refluxed for 18 h in 10 mL of glacial AcOH. Sodium acetate was separated by decantation. The reaction mixture was left for 24 h at ambient temperature, and the precipitate (**5a–g**) was filtered off and purified by recrystallization from 2-PrOH/DMF.

Compounds (Yield) **5a** [10(a,g,h,i)] (76%), **5b** [10(b,e)] (54%), **5c** [10(a,g)] (12%), **5d** [10(b,d,g)] (49%), **5e** [10(g)] (24%), **5f** [10(b,c)] (53%), **5g** [10(b,f)] (23%) have been described in the literature.

4,4′-Bis(5-phenyl-6-carbethoxy-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidinyl-2-ylmethylene)benzene (6a). A mixture of **1a** 2.76 g (0.01 mole), anhydrous sodium acetate 1.0 g (0.015 mole), chloroacetic acid 1.0 g (0.011 mole), terephthalic aldehyde 0.67 g (0,005 mole) at 10 mL glacial AcOH was thoroughly sealed in a tube and allowed to stand at 180°C for 12 h. The precipitate formed was filtered off, washed with 100 mL of hot water, and purified with recrystallization from DMF.

Red solid, yield 76%, mp: <300°C (DMF); IR (KBr): ν 1560 (C=N), 1715 (C=O) 2990 (CH) cm^{-1}. ^1H NMR (400 MHz, CF_3COOD): δ = 8.31 [s, 2 H, $C_6H_4(CH)_2$], 7.81 [s, 4 H, C_6H_4], 7.47 [m, 10 H, 2 × C_6H_5], 6.52 [s, 2 H, 2 × C_6H_5CH], 4.34 [m, 4 H, 2 × CH_2CH_3], 2.75 [s, 6 H, 2 × $NCCH_3$], 1.32 [t, 6 H, 2 × CH_2CH_3]. *Anal*. Calcd. for $C_{40}H_{34}N_4O_6S_2$: C, 65.74; H, 4.69; N, 7.67. Found: C, 64.45; H, 4.61; N, 7.81.

X-ray structure determination of 5a. ***Crystal data.*** $C_{10}H_7NO_2S$, M = 205.2, monoclinic, a = 9.5115(6), b 11.6786(7), c = 8.2306(6) Å, β = 96.146(4)°, V = 909.0(1) $Å^3$, Z = 4, d = 1.50 g cm^{-1}, space group $P2_1/c$ (N 14), μ = 3.24 cm^{-1}, $F(000)$ = 424, crystal size ca. 0.12 × 0.44 × 0.45 mm^3. All crystallographic measurements were performed at 293°C on a Bruker Apex II CCD diffractometer. The intensity data were collected within the range $2.8 < \theta < 26.3°$ ($-11 < h < 11$, $-14 < k < 14$, $-10 < l < 8$) using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Intensities of 6416 reflections (1846 unique, R_{int} = 0.003) were measured. Data were corrected for Lorentz and polarisation effects and an absorption correction using the Sadabs procedure was applied [13]. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic

approximation using the CRYSTALS program package [14]. In the refinement 1313 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the different Fourier maps and refined isotropically). Convergence was obtained at $R = 0.029$ and $R_w = 0.030$, GOF = 1.109 (155 refined parameters; obs./variabl. 8.5). Chebushev weighting scheme [15] with parameters 1.59, 1.50, 1.79, 0.55, and 0.47 was used.

Acknowledgments. This work was supported by Fundamental Researchers State Fund (F25.3/023).

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