ORGANIC LETTERS

2007
Vol. 9, No. 21
4215−4218

A One-Step Fusion of 1,3-Thiazine and Pyrimidine Cycles

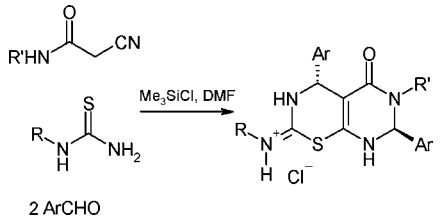
Sergey V. Ryabukhin,*[,†,‡] Andrey S. Plaskon,[†,‡] Eugeniy N. Ostapchuk,[†] Dmitriy M. Volochnyuk,[†,§] Oleg V. Shishkin,[¶] Alexander N. Shivanyuk,[‡] and Andrey A. Tolmachev[‡]

Enamine Ltd., 23 A. Matrosova st., 01103 Kyiv, Ukraine, National Taras Shevchenko University, 62 Volodymyrska st., 01033 Kyiv, Ukraine, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska st., 02094 Kyiv, Ukraine, and STC "Institute for Single Crystals", National Academy of Sciences of Ukraine, 60 Lenina ave., 61001 Kharkiv, Ukraine

ryabukhin@mail.enamine.net

Received July 25, 2007

ABSTRACT



The chlorotrimethylsilane-promoted Biginelli type reactions of aldehydes, thiourea, and cyanoketones led to a diverse set of tetrahydropyrimidine-2(1*H*)-thiones. Under similar conditions, thioureas, benzaldehyde, and cyanoacetamide reacted to give first representatives of hexahydro-5*H*-pyrimido[5,4-*e*][1,3]thiazin-5-ones in high preparative yield.

In multicomponent reactions (MCR), three or more reactants come together in a single reaction vessel to form new products that contain structural units of all the components. This type of reaction becomes increasingly important in organic and medicinal chemistry because it allows on to obtain highly sophisticated polyfunctional molecules through simple one-pot procedures. Multicomponent reactions have been successfully employed to generate highly diverse combinatorial libraries for high-throughput screening of biological and pharmacological activities. The use of three or more building blocks in a one-pot, high-yield multicomponent reaction leads to a wide structural and functional diversity combined with excellent combinatorial efficacy. Over the past decade, industrial and academics research has made powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial synthesis.[1]

The Biginelli reaction is typically the acid-catalyzed one-pot multicomponent cyclocondensation of an aldehyde, a β-ketoester, and a urea, resulting in various dihydropyrimidines. The latter have shown to be efficient calcium channel modulators, mitotic kinesine inhibitors, adrenergic receptor antagonists, and antibacterial and antiviral agents.[2] Such a wide spectrum of biological activity allows consideration of the dihydropyrimidine structural unit as one of the most important drug-like scaffolds. It has been found that the Biginelli reaction can be efficiently promoted by Lewis acids such as BF_3 OEt_2, LaX_3 (X = Cl, OTf), $Yb(OTf)_3$, InX_3 (X

† Enamine Ltd.
‡ National Taras Shevchenko University.
§ Institute of Organic Chemistry, National Academy of Sciences of Ukraine.
¶ STC, National Academy of Sciences of Ukraine.

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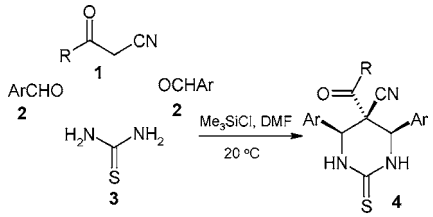
10.1021/ol701782v CCC: $37.00
Published on Web 09/12/2007

= Cl, Br), $ZrCl_4$, BiX_3 (X = Cl, OTf), LiX (X = Br, ClO_4), $Mn(OAc)_3$, CAN, $FeCl_3 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $RuCl_3$, and SmI_2 etc. as catalyst.[3] Me_3SiCl,[4] microwave assistance,[5] solid- and fluorophase techniques[6] have also been widely employed for the facilitation of the Biginelli reactions.

We considered ketonitriles and cyanoacetamides as promising *CH*-active components for the Biginelli cyclocondensations since the dihydropyrimidines obtained would contain a nitrile group which can be easily converted to amine, tetrazole, guanidine, amidine, and other pharmacophore structural units. On the basis of our previous studies[5a,7] of various condensation reactions, we chose trimethylchlorosilane as a promoter and water scavenger.

The model Biginelli reactions of ketonitriles **1a**,**b**, benzaldehydes **2a**−**c**, and thiourea **3** (1:2:1 molar ratio) in the presence of TMSCl in DMF at 25 °C[8] led to tetrahydropyrimidine-2(1*H*)-thiones **4** in nearly quantitative yields (Scheme 1), whereas less nucleophilic urea did not react under these conditions. Compounds of type **4** have been obtained earlier through the stepwise procedure involving the formation of the benzylidene derivatives.[9] Very recently, condensation of some carbonyl compounds (dimedone, barbituric acid, and pyrazolone derivatives), thiourea, and aromatic aldehydes has been reported to yield similar compounds, whereas the reaction of N-substituted (thio)-ureas with cyanoketones and benzaldehyde (TMSCl, DMF) gives exclusively the benzylidene compounds.[10] The structure and composition of compounds **4** were established on the basis of NMR spectra, LCMS data, and elemental analysis.

Scheme 1. One-Pot Synthesis of Tetrahydropyrimidine-2(1*H*)-thiones **4** from Ketonitriles, Thiourea, and Benzaldehydes



1a: R = Ph **1b**: R = *t*-Bu
2a: Ar = Ph **2b**: Ar = *p*-$OMeC_6H_4$
2c: Ar = *p*-ClC_6H_4

N	R	Ar	Yield %
4a	Ph	*p*-$OMeC_6H_4$	92
4b	Ph	*p*-ClC_6H_4	96
4c	*t*-Bu	Ph	87
4d	*t*-Bu	*p*-$OMeC_6H_4$	85

The structure of compound **4a** was unambiguously determined by single-crystal X-ray analysis.[11,12] In the crystalline state, the tetrahydropyrimidine cycle of the molecule **4a** adopts a sofa conformation (Figure 1a). The deviation of carbon atom C(3) from the rms plane of the other atoms of the cycle is −0.72 Å. In the crystalline state, molecules **4a**

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(8) General procedure for the synthesis of tetrahydropyrimidine-2(1*H*)-thiones **4**: To a solution of ketonitrile **1** (4 mmol), aldehyde **2** (8 mmol), and thiourea **3** (6 mmol) in dry DMF (10 mL) was added dropwise chlorotrimethylsilane (16 mmol), and the solution was sonicated for 1 h at rt for homogenization of the reaction mixture. After standing for 2 days at rt, the reaction mixture was poured into water (20−30 mL) and the suspension formed was sonicated for 1 h to maximize the removal of DMF from the suspension. The precipitate formed was filtered off and washed with a small amount of *i*-PrOH. First, filtrate was evaporated under reduced pressure, and the residue was treated with a small amount of *i*-PrOH. Recrystallization of both portions yielded compounds **4a**−**d** (see Scheme 1).

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(11) Selected crystallographic data for **4a**: $C_{26}H_{23}N_3O_3S$, monoclinic $P2_1/n$, a = 16.405(6), b = 8.826(2), c = 16.643(1) Å, β = 99.18(1)°, V = 2379(1) Å^3, Z = 4, d_{calcd} = 1.277 g/cm^3, μ(Mo Kα) = 0.168 mm^{-1}, $F(000)$ = 960, R_1 = 0.057 (3630 refln $F > 4\sigma(F)$), wR_2 = 0.185 (6605 refln), S = 0.995.

(12) Sheldrick, G. M. *SHELXTL PLUS*, revision 5.1; PC version. A system of computer programs for the determination of crystal structure from X-ray diffraction data.

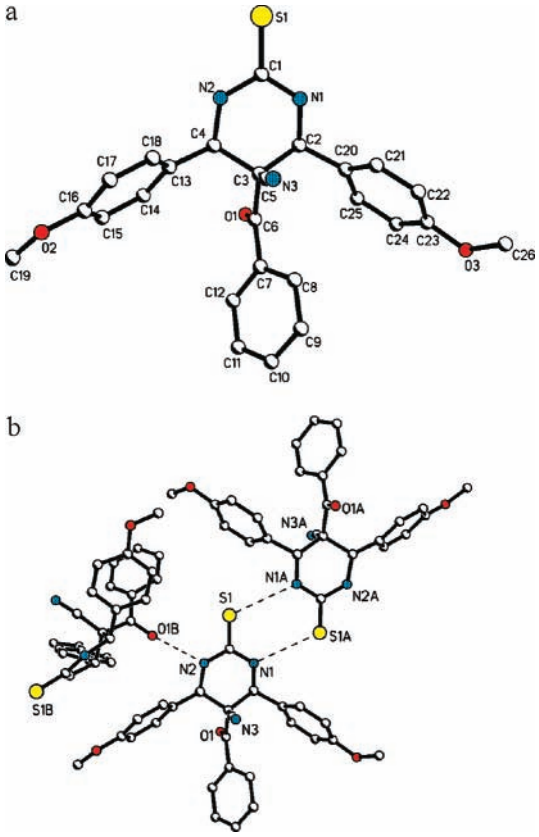


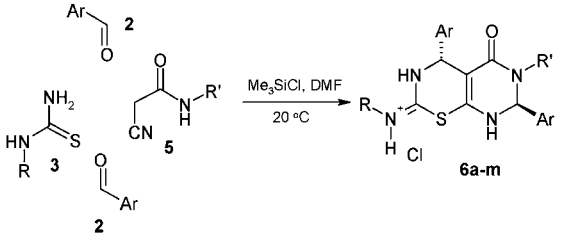
Figure 1. Single-crystal X-ray structure of **4a**: (a) molecular structure; (b) fragment of crystal packing.

form infinite sheets stabilized by intermolecular hydrogen bonds N−H···S and N−H···O (Figure 1b).

Unexpectedly, the reaction of cyanoacetamides **5a**−**f**, which are analogues of cyanoketones, with thioureas **3a**−**g** and benzaldehydes **2a**−**c** (DMF, TMSCl) at various molar ratios led to hydrochlorides of 2-imino-2,3,4,6,7,8-hexahydro-5*H*-pyrimido[5,4-*e*][1,3]thiazin-5-ones **6a**−**m**, which are the first representatives of a thiazinopyrimidine heterocyclic system.[13] Compounds **6** were isolated in 56−92% yield through precipitation with water and simple recrystallization (Scheme 2). The highest yields of heterocycles were attained when the reagents were taken in a stoichiometric (1:1:2) molar ratio. The composition of compounds **6** was determined by LCMS and elemental analysis; however, the exact structure could not be unambiguously revealed on the basis of NMR data.

Many attempts to grow single crystals of compounds **6** were initially unsuccessful because of low solubility in

Scheme 2. One-Pot Synthesis of 2-Imino-2,3,4,6,7,8-hexahydro-5*H*-pyrimido[5,4-*e*][1,3]thiazin-5-ones **6** from Cyanoacetamides, Thioureas, and Benzaldehydes



2a: Ar = Ph **2b**: Ar = *p*-$OMeC_6H_4$ **2c**: Ar = *p*-ClC_6H_4
3a: R' = R'' = H **3b**: R' = Me, R'' = H **3c**: R' = Et, R'' = H
3d: R' = Ph, R'' = H **3e**: R' = $(CH_2)_2OMe$, R'' = H
3f: R' = $(CH_2)_3OEt$, R'' = H **3g**: R' = CH_2THF, R'' = H
5a: R = H **5b**: R = Me **5c**: R = Bn
5d: R = *p*-ClC_6H_4 **5e**: R = $(CH_2)_2OMe$ **5f**: R = $(CH_2)_3OEt$

N	R	R'	Ar	Yield %
6a	H	H	Ph	85
6b	Me	H	Ph	73
6c	H	Me	Ph	88
6d	Et	Me	Ph	61
6e	Ph	Me	Ph	75
6f	H	Bn	Ph	68
6g	H	*p*-ClC_6H_4	*p*-ClC_6H_4	92
6h	Ph	*p*-ClC_6H_4	*p*-$OMeC_6H_4$	86
6i	$(CH_2)_2OMe$	$(CH_2)_2OMe$	Ph	72
6j	CH_2THF	$(CH_2)_2OMe$	Ph	59
6k	$(CH_2)_2OMe$	$(CH_2)_3OEt$	Ph	64
6l	$(CH_2)_3OEt$	$(CH_2)_3OEt$	Ph	59
6m	CH_2THF	$(CH_2)_3OEt$	Ph	56

common organic solvents.[14] This was the main reason for the synthesis of more soluble analogues **6i**−**m**. Slow evaporation of the solution of compound **6j** in EtOH−Et_2O mixture gave colorless crystals suitable for single-crystal X-ray diffraction study. In the crystalline state, the tetrahydropyrimidine cycle of the molecule **6j** adopts a sofa conformation (Figure 2a). The deviation of atom C(1) from the rms plane of other atoms of the cycle was found to be 0.45 Å. The phenyl ring bound to C(1) is located in the axial position, being nearly perpendicular to bond N(1)−C(1).

The 1,3-thiazine cycle of the molecule **6j** adopts a boat conformation (Figure 2a). The deviations of atoms C(4) and S(1) from the rms plane of the other atoms of the cycle are 0.42 and 0.33 Å, respectively. The phenyl substituent bound to C(4) is situated in a pseudo-equatorial position, being virtually coplanar to bonds C(3)−C(4). The tetrahydro-

(13) General procedure for the synthesis of compounds **6**: To a solution of cyanoacetamide **5** (4 mmol), aldehyde **2** (8 mmol), and thiourea **3** (4.4−6 mmol) in dry DMF (10 mL) was added dropwise chlorotrimethylsilane (16 mmol), and the solution was sonicated for 1 h at rt. After stirring for 2−3 days at rt, the reaction mixture was poured into water (20−30 mL). The suspension formed was sonicated rt for 1 h, and the precipitate formed was filtered off and washed with a small amount of *i*-PrOH. The filtrate was evaporated under reduced pressure, and the residue was treated with a small amount of *i*-PrOH or Et_2O. Recrystallization of both portions from appropriate solvent yielded targeted compounds **6a**−**m** (see Scheme 2).

(14) Selected crystallographic data for **6j**: $C_{26}H_{31}N_4O_3S^+Cl^-$, monoclinic $P2_1/n$, a = 9.675(1), b = 20.321(5), c = 13.433(2) Å, β = 103.72(1)°, V = 2565.7(8) Å^3, Z = 4, d_{calcd} = 1.333 g/cm^3, μ(Mo Kα) = 0.266 mm^{-1}, $F(000)$ = 1088, R_1 = 0.047 (3867 refln $F > 4\sigma(F)$), wR_2 = 0.138 (5777 independent refln), S = 0.969.

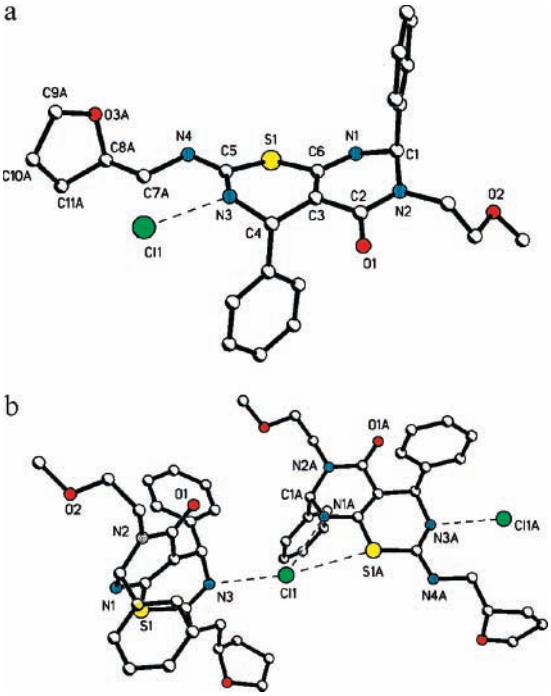


Figure 2. Single-crystal X-ray structure of compound **6j**: (a) molecular structure; (b) fragment of crystal packing. Hydrogen atoms are not shown; hydrogen bonds are indicated by dashed lines.

furanemethyl fragment is disordered over two positions in which it adopts an envelope and twist conformation.

The location of hydrogen atoms at nitrogen atoms N(3) and N(4) as well as the lengths of bonds N(3)−C(5) (1.311-(2) Å) and N(4)−C(5) (1.307(2) Å) that are comparable with an average length of the N=C(sp^2) bond (1.316 Å)[15] indicate that the positive charge of the cation is localized on protonated fragment N(3)−C5−N4. The cation and chloride ion form strong hydrogen bonds (N−H···Cl) which in combination with intermolecular N−H···O hydrogen bonding result in infinite molecular chains (Figure 2b) along the crystallographic axis *c*.

The ^{1}H NMR spectra of the reaction mixtures contain one set of signals for compounds **6**, indicating the selective formation of one diastereomer, which is a racemic mixture of *RS*′ and *SR*′ enantiomers. No traces of the other diastereomer (*RR*′,*SS*′) were detected by NMR spectrometry.

In conclusion, the TMSCl-mediated Biginelli type reaction of cyanoketones with thiourea and benzaldehydes furnishes dihydropyrimidinenitriles in high preparative yield and excellent purity. Serendipitously, a similar reaction of cyanoacetamides with benzaldehyde and thioureas leads to the first representatives of the thiazinopyrimidine heterocyclic system. In contrast, urea and its N-substituted derivatives do not give cyclic products in the Biginelli type reaction, most probably due to the lower nucleophilicity of the oxygen atom compared to that of the sulfur atom. Apparently high yields and simple purification procedures of the TMSCl-mediated Biginelli type heterocyclizations make them suitable for generating combinatorial libraries of dihydropyrimidines and thiazinopyrimidines. Compounds **4** and **6** bearing highly reactive functional groups are promising starting materials for rational design of more sophisticated functional molecules.

Acknowledgment. The authors acknowledge V. V. Polovinko (Enamine Ltd.) for spectral measurements, and Mr. D. N. Mikitenko for helpful discussions and suggestions.

Supporting Information Available: Experimental procedures and characterization data for compounds obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

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