Tetrahedron Letters 51 (2010) 2095–2098

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Unexpected alternative direction of a Biginelli-like multicomponent reaction with 3-amino-1,2,4-triazole as the urea component

Nikolay Yu. Gorobets [a,b], Yuriy V. Sedash [a], Konstantin S. Ostras [a], Oleg V. Zaremba [c], Svetlana V. Shishkina [a], Vyacheslav N. Baumer [a], Oleg V. Shishkin [a], Sergiy M. Kovalenko [c], Sergey M. Desenko [a], Erik V. Van der Eycken [b,*]

[a] SSI 'Institute for Single Crystals' of National Academy of Sciences of Ukraine, Lenin Ave. 60, Kharkiv 61001, Ukraine
[b] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Katholieke Universiteit Leuven, Celestijnenlaan 200F, Leuven B-3001, Belgium
[c] National University of Pharmacy, Pushkinska Str. 53, Kharkiv 61002, Ukraine

ARTICLE INFO

Article history:
Received 24 December 2009
Revised 4 February 2010
Accepted 5 February 2010
Available online 11 February 2010

Keywords:
Biginelli condensation
Multicomponent reaction
3-Amino-1,2,4-triazole
Microwave-assisted organic synthesis

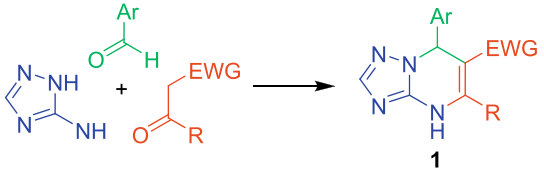
ABSTRACT

A Biginelli-like three-component condensation using 3-amino-1,2,4-triazole as urea component resulted in an unexpected alternative direction of the tetrahydropyrimidine ring formation.

1. Introduction

A variety of bioactive compounds[1] can be obtained via a Biginelli-like condensation using an aminoazole as the urea component.[1,2] It could be assumed from the literature that these reactions lead to partially reduced azolopyri(mi)dines where the aldehyde component is attached exclusively to the endocyclic nitrogen or carbon of the azole ring. Thus, in the case of 3-amino-1,2,4-triazole (Scheme 1), compounds of structure **1** were generally reported to be formed[3] with the exception of a few examples.[2,4]

The aim of this work was the investigation of the application of 3-amino-1,2,4-triazole and different salicylic aldehydes in a Biginelli-like three-component condensation. The presence of an *ortho*-hydroxyphenyl group in the aldehyde should allow for the formation of an oxygen bridge[5] resulting in a novel polyheterocyclic system **2** (Fig. 1; ethyl acetoacetate as the third component). However, our first experiments using salicylic aldehyde, 3-amino-1,2,4-triazole, and ethyl acetoacetate in the presence of aqueous HCl at room temperature or under reflux conditions resulted in the formation of the known[6] binary compound **3** next to the imine **4**[7] which was formed as a precipitate immediately after mixing the reagents in ethanol (Fig. 1). To avoid the formation of binary product **3** we decided to use acetone instead of the bifunctional ethyl acetoacetate. However, to our surprise and in contrast to the literature data,[3] an alternative direction of this Biginelli-like reaction was observed. When the condensation was performed in aqueous HCl for 3 h under reflux conditions, compound **5**



Scheme 1. General outcome of a Biginelli-like condensation reaction with 3-amino-1,2,4-triazole.

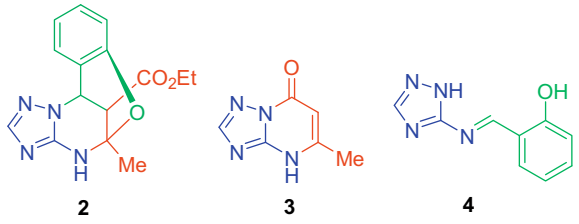


Figure 1. The expected product **2** and the binary by-products **3** and **4**.

* Corresponding author. Tel.: + 32 16 327406.
E-mail address: erik.vandereycken@chem.kuleuven.be (E.V. Van der Eycken).

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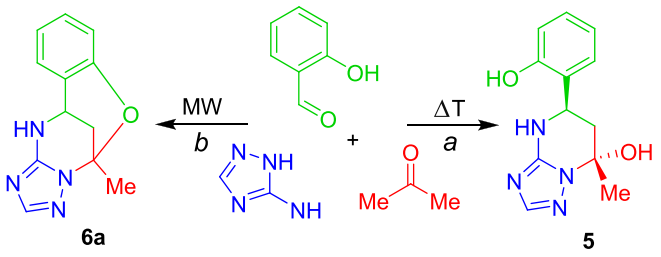
doi:10.1016/j.tetlet.2010.02.045



Scheme 2. Products formed depending on the applied conditions: (a) MeOH, HCl (4 N in dioxane), 40 °C, 16 h; (b) EtOH, HCl (4 N in dioxane), MW 150 °C, 30 min.

(structure as depicted in Scheme 2) was obtained in a low yield of 25% next to the imine **4** (Fig. 1) as the major side compound, while under microwave irradiation at a ceiling temperature of 170 °C for 30 min the oxygen-bridged compound **6a** (structure as depicted in Scheme 2) was formed in 29% yield. Clearly, in both cases, the aldehyde component reacted with the exocyclic aminogroup of the 3-amino-1,2,4-triazole instead of the endocyclic nitrogen of the triazole ring (Scheme 2). Also when preformed imine **4** (Fig. 1) was used as the starting material, the same reaction pattern was observed. Intrigued by this observation we tried to optimize the reaction conditions (Table 1). To exclude water from the reaction mixture a dioxane solution of HCl was used (4 N) while the reaction was performed in methanol at 40 °C for 16 h. A moderate yield of 60% was obtained for compound **5** when 0.1 equiv of HCl was used (Table 1). As recorded in our preliminary experiments, oxygen bridge formation requires higher temperatures, and therefore the synthesis of **6a** was optimized using microwave irradiation. The reaction was performed in ethanol with 0.3 equiv of HCl (4 N in dioxane) and upon microwave irradiation at a ceiling temperature of 150 °C and a maximum power of 300 W for 30 min to yield the desired compound **6a** in 47 % yield (Scheme 2). Interestingly when water compatible Lewis acids[8], for example, $Yb(OTf)_3$ and $Sc(OTf)_3$ (1.0–15 mol %) were used, lower yields were obtained. The scope and limitations of the optimized microwave-assisted protocol were further evaluated for the synthesis of oxygen-bridged compounds **6b–g** applying a number of commercially available salicylic aldehydes (Table 2). Yields ranging between 33% and 51% were obtained upon precipitation next to an array of unidentified side compounds being present in the mother liquor. Under similar reaction conditions butan-2-one afforded a mixture of three isomers **7a–c** obtained in 42 % yield in a ratio 3:3:1 for **7a**:**7b**:**7c**, as was established by LC/MS (Fig. 2). These compounds could be separated by preparative HPLC. With 3-methylbutan-2-one and 4-methylacetophenone the corresponding bridged compounds **8** and **9** were formed, although they were isolated upon precipitation in rather poor yields of 25% and 21%, respectively, due to incomplete reaction and imine formation.

The structures of compounds **5** and **6c** were proven via single crystal X-ray diffraction study, clearly showing that for compound **5** the aromatic ring and the methyl group are cis-orientated (Fig. 3). The structures of the diastereoisomers **7b** and **7c** were determined based on the differences in NOESY correlations of the methyl group at position 13. In the case of the compound **7c**, correlations were observed with the protons of the aryl ring, while for **7b** such correlations are absent (Fig. 2, see Supplementary data for details).

Next we investigated the application of different carbonyl compounds. Thus, 16 h of stirring of an equimolar mixture of salicylic aldehyde and 3-amino-1,2,4-triazole with 1.1 equiv of ethyl acetoacetate in the presence of 0.1 equiv of HCl (solution in dioxane) in absolute ethanol resulted in the formation of dihydroxy derivative **10a** (Fig. 2) that was isolated in a yield of 67% after precipitation (conditions (a) of Scheme 2 were applied). In this case absolute ethanol was used instead of methanol to avoid transesterification. The relative configuration at the stereocenters was assigned by NMR as being 5*R*,6*S*,7*S*. Compound **10a** was observed to slowly undergo isomerization into diastereoisomer **10b** (5*R*,6*R*,7*S*) in DMSO-d_6 solution during NMR-measurement.[9]

When 3-acetyl-dihydrofuran-2(3*H*)-one was used in this Biginelli-like multicomponent reaction (MeOH, 0.1 equiv of HCl, 40 °C, 16 h) a regio- and stereoselective formation of the spiropyrimidine **11** was observed which could be isolated in 71% yield.[9]

In summary, we can conclude that for the investigated examples the 3-amino-1,2,4-triazole behaves differently compared to other aminoazoles in the Biginelli-like multicomponent reaction. The aldehyde component reacted with the exocyclic aminogroup of the 3-amino-1,2,4-triazole instead of the endocyclic nitrogen of the triazole ring. Optimized reaction conditions were obtained under conventional and microwave heating using salicylic aldehydes. An efficient microwave-assisted procedure was developed to generate the corresponding oxygen-bridged compounds.

2. Experimental section

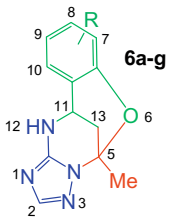
2.1. Synthesis of (5*R*,7*S*)-5-(2-hydroxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (5)

Scheme 2, Reaction conditions (a): To a mixture of salicylic aldehyde (15 mmol), 3-amino-1,2,4-triazole (15 mmol), and acetone (45 mmol, 3.3 mL) in MeOH (15 mL) in a sealed round-bottomed flask, HCl (1.5 mmol, 0.38 mL, 4 N solution in dioxane) was added. The mixture was stirred at 40 °C for 16 h, then cooled to room temperature, and the precipitate was filtered off, washed with MeOH (5 mL) and ether (3 × 5 mL), and dried. The compound was obtained in 60% yield. The compounds **10a** and **11** were

Table 1
Variation of the catalyst amounts in the synthesis of **5** and **6b** under conditions (a) and (s) correspondingly

Reaction conditions (a)			Reaction conditions (b)		
Entry	HCl in dioxane (4 N solution) (equiv)	Yield (%)	Entry	HCl in dioxane (4 N solution) (equiv)	Yield (%)
1	0.05	55	1	0.1	41
2	0.1	60	2	0.3	**47**
3	0.3	47	3	0.5	34
4	0.5	23	4	1.0	0

Table 2
Microwave-assisted synthesis of oxygen-bridged heterocycles **6a–g**



Product	R	Isolated yield (%)
6a	H	47
6b	7-MeO	47
6c	7-EtO	51
6d	8-MeO	33
6e	9-Me	50
6f	9-Cl	49
6g	9-Br	50

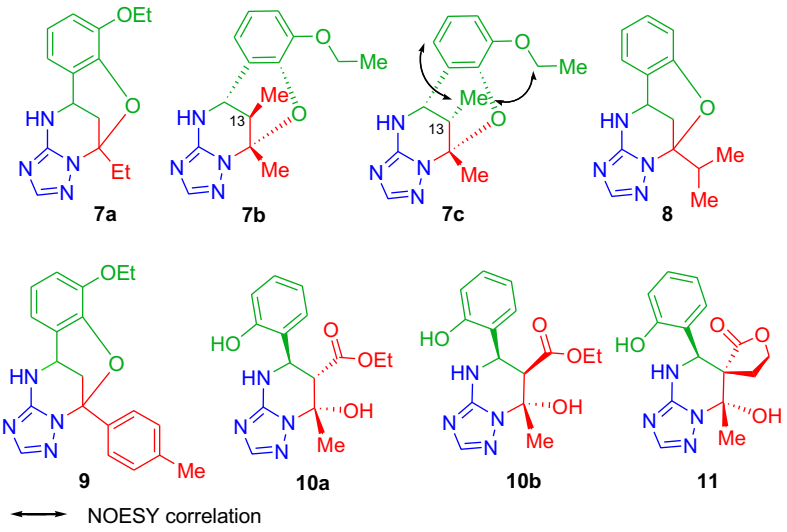


Figure 2. Structures of products **7a–c**, **8**, **9**, **10a**, **b**, and **11**.

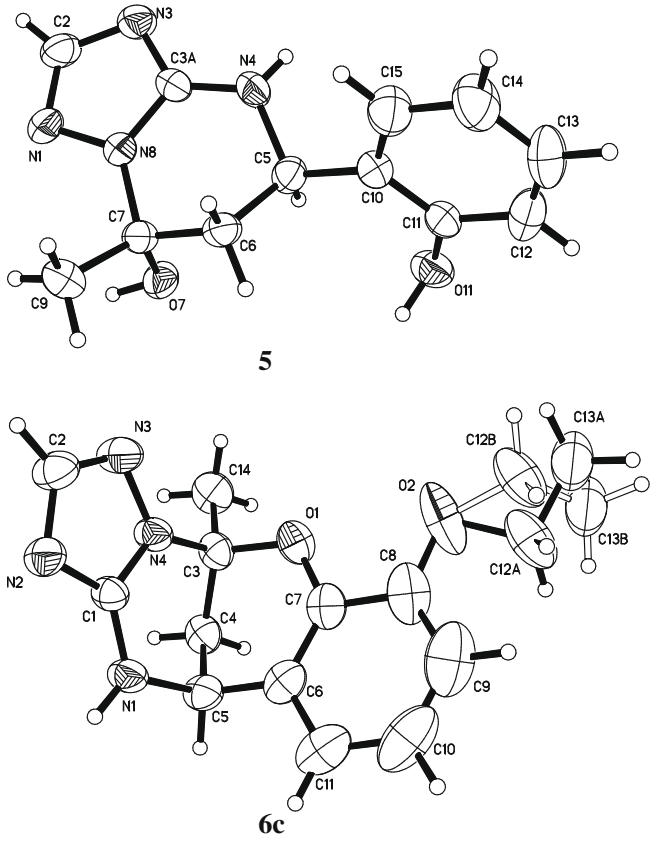


Figure 3. Molecular structures (X-ray diffraction data) of compounds **5** and **6c**.

obtained similarly using 1.1 equiv of the corresponding carbonyl compound. Absolute EtOH (15 mL) was used as solvent for the synthesis of **10a**. Characterization data for the mentioned products are given in the Supplementary data.

2.2. Synthesis of 5-methyl-11,12-dihydro-5,11-methano[1,2,4]triazolo[1,5-*c*][1,3,5]-benzoxadiazocine (6a)

Scheme 2, Reaction conditions (b). To a mixture of salicylic aldehyde (3.0 mmol), 3-amino-1,2,4-triazole (3.0 mmol), and acetone (9.0 mmol, 0.66 mL) in MeOH (4 mL) in a microwave process vial, HCl (0.9 mmol, 0.23 mL, 4 N solution in dioxane) was added. The mixture was irradiated at a ceiling temperature of 150 °C and a maximum power of 300 W for 30 min (multimode Milestone MicroSYNTH microwave reactor). The reaction mixture was cooled by an air flow and left being stirred for 24 h at room temperature to reach complete precipitation. The precipitate was filtered off, washed with MeOH (1 mL) and ether (3 × 1 mL), and dried. The compound was obtained in 60% yield. The compounds **6b–g**, **7a–c**, **8**, and **9** were obtained in a similar way (see the Supplementary data for details).

Acknowledgments

Dr. Nikolay Yu. Gorobets performed the research partially as an International Scholar at K.U. Leuven. Support was provided by the F.W.O. (Fund for Scientific Research—Flanders (Belgium)).

Supplementary data

Supplementary data (experimental procedures and characterization of new compounds including spectral, analytical and X-ray diffraction study data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.045.

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9. For a detailed study of compounds **10a**, **b**, and**11** using HSQC, HMBC, COSY, and NOESY experiments see the Supplementary data.