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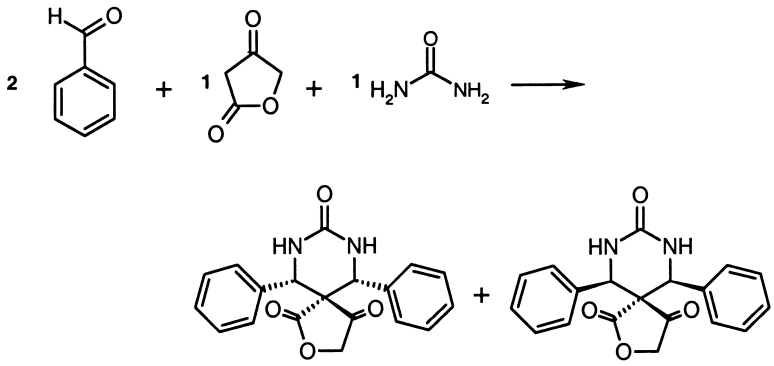

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New Regioselective Multicomponent Reaction: One Pot Synthesis of Spiro Heterobicyclic Aliphatic Rings

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In the context of our high-throughput organic synthesis program, we have studied the reactivity of special β-keto esters toward the Biginelli reaction. We have found that a cyclic β-keto ester reacts with one molecule of urea and two molecules of aldehyde to give a new family of spiro heterobicyclic aliphatic rings in good yields. Interestingly, the Biginelli product was not detected. After analysis of products using HPLC, ^{1}H NMR, and ^{13}C NMR, we have found that the reaction is driven by a regio-specific condensation of two molecules of aldehyde with the other reagents to afford only products harboring substituents exclusively in cis configuration. Monte Carlo minimization studies using MM2 force field suggest that cis products are energetically more stable than the trans counterparts. Together with previously reported data, these results suggest that the trans products were not obtained as result of steric hindrance produced by the equatorial position of one of the ring substituents. This new reaction is useful for high-throughput organic synthesis. Indeed, the new scaffold can be used to introduce additional groups in the molecules through remaining functional groups by a "domino strategy".

Introduction

During the last 10 years pharmaceutical companies have invested significant efforts in developing robotics and miniaturization for biological screening purposes. As result of these efforts, the capacity of biologists to perform in vitro high-throughput screening of chemicals for drug discovery was dramatically improved.[1] The main limitation of this new screening technology lies in the capacity of the chemists to furnish biologists with a great diversity and number of products.[2]

Traditionally, drug discovery involved the optimization of lead structures, most likely derived from biological sources, through a multistep process of serial synthesis and screening. This approach is extremely costly, as each compound will have to be individually synthesized in solution by a synthetic chemist. The need to find more cost-effective methods of drug development, combined with the recent advances in robotic screening that enable the testing of hundreds of thousands of products per year, has led pharmaceutical companies to examine combinatorial synthetic strategies as means of accelerating drug discovery programs and increasing the chemical diversity of their compound libraries.[3]

Chemists from academia are presently conscious that novel synthetic tools must be developed in order to meet the increasing requirements of the high-throughput biological screening technology. For this purpose, the use of robotics in organic synthesis may significantly improve the diversity of synthetic libraries and may allow the finding of new organic reactions.[4] The emerging technology, so-called combinatorial chemistry, is based on the simple premise that the greater the diversity of compounds tested, the better the chance of finding one that can be developed into a drug or other industrial lead. Although it is theoretically not limited to any specific family of chemical species, the scopes of this approach are actually limited as result of the restrained organic reactions available for synthesis on solid supports and by the limited quantity of available multireagent organic reactions.[5] A main goal of the present work is to discover and develop novel reactions for extending the scope of combinatorial chemistry. Specifically, multicomponent reactions are of great interest for high-throughput synthesis as the different components can be automatically fed onto a robot and products are obtained in one pot.

We have studied the reactivity of cyclic β-keto esters toward the Biginelli reaction.[6] Surprisingly, we have found that the aliphatic five-member ring β-keto ester reacts with 1 equiv of urea and 2 equiv of aldehyde in a regioselective manner to give a family of novel spiro heterobicyclic aliphatic ring compounds in good yields. This novel multicomponent reaction is useful for high-throughput organic synthesis.

Results and Discussion

The original aim of this work was to extend the scope of the well-known multicomponent Biginelli reaction[6] to fused bicyclic rings (see Figure 1).

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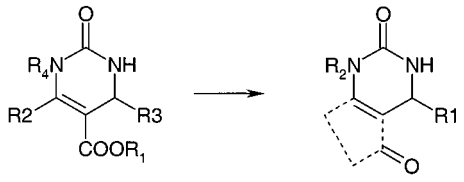

Figure 1. Proposed extension of Biginelli reaction to fused bicyclic rings.

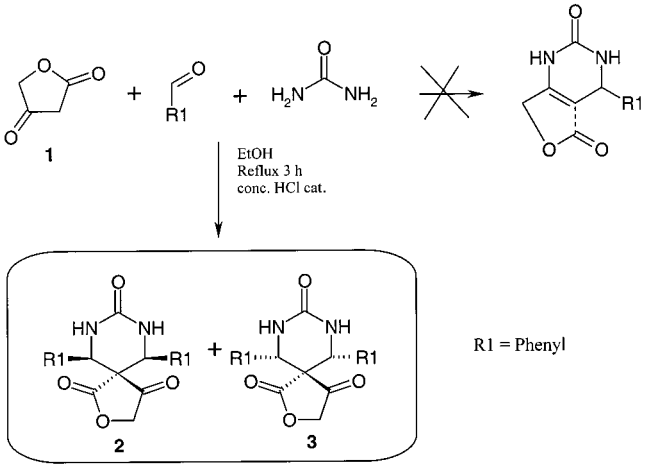

Figure 2. Novel multicomponent reaction of pseudo-four components to obtain a new spiro heterobicyclic system.

We raised the question whether a fused bicyclic ring can be obtained in one pot by reacting a five-member ring β-ketolactone with 1 equiv of urea and 1 equiv of aldehyde to extend the classical Biginelli multicomponent reaction (see Figure 2). To answer to this question, tetronic acid **1** was reacted with benzaldehyde and urea under the usual conditions for Biginelli reaction.

Interestingly, after analysis of products, the expected Biginelli product was not detected. However, we have found that one molecule of tetronic acid reacted with two molecules of aldehyde and one molecule of urea to afford exclusively a spiro heterobicyclic aliphatic ring harboring two substituents generated from the former aldehyde (see products **2** and **3** in Figure 2). The HPLC analysis of the product indicates the presence of a mixture of two isomers with the same molecular weight. The ratio of the isomers was close to 1:1 as demonstrated by HPLC integration of the crude mixture (see Figure 3).

The isomers were isolated and analyzed by mass spectra and NMR, which shows that both are symmetrical, with only one set of signals for the CHR_1 moiety and a singlet for the methylene protons (see Figure 4). This excludes a trans orientation of the R_1 groups (from the aldehyde precursor). These cis isomers most probably have axial ring CHs and equatorial R_1 groups (see calculations in Figure 5 below).

The final identification of the two isomers was performed using HMBC spectra (two-dimensional long-range $^1H \times {}^{13}C$ correlation). It is well-known[7] that vicinal (three-bond) C−H coupling constants follow a Karplus-like relationship and therefore are expected to be larger for an anti than for a gauche arrangement (180° and 60° dihedral angles, respectively).

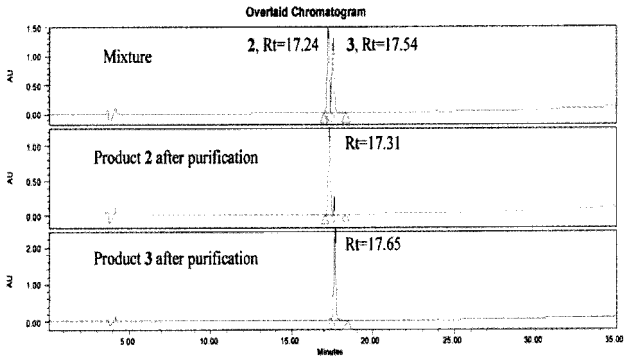

Figure 3. HPLC of crude precipitate products **2** + **3** (upper chromatogram), purified product **2** (middle chromatogram), and purified product **3** (lower chromatogram). For gradient conditions, see Experimental Section.

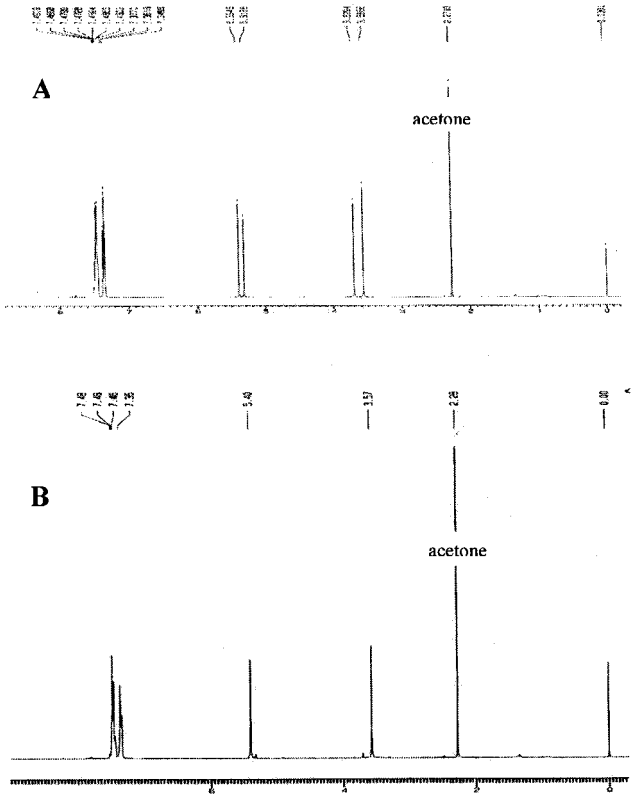

Figure 4. ^1H NMR of the mixture of products **2** + **3** (panel A) and purified product **2**.

In agreement with this expectation, we found that the intensity of the cross-peaks between the ring CH protons and the carbonyls of the five-member ring are quite different. Indeed, in isomer **3** the stronger cross-peak is for the interaction with the ketone carbonyl, indicating that this is the substituent in the axial orientation; conversely, in the isomer **2**, the stronger cross-peak is for the interaction with the lactone carbonyl (see Figures 4−5 for NMR).

Therefore, this new multicomponent reaction is driven by a regio-specific condensation of four components. This was already observed for other one-pot condensations which led exclusively to cis protons in generated fused polycyclic rings.[8] The order of the multicomponent reaction is pseudo-4 (ΨMCR4). Indeed, four molecules react to give a single product, but two of them belong to the same product (aldehyde).

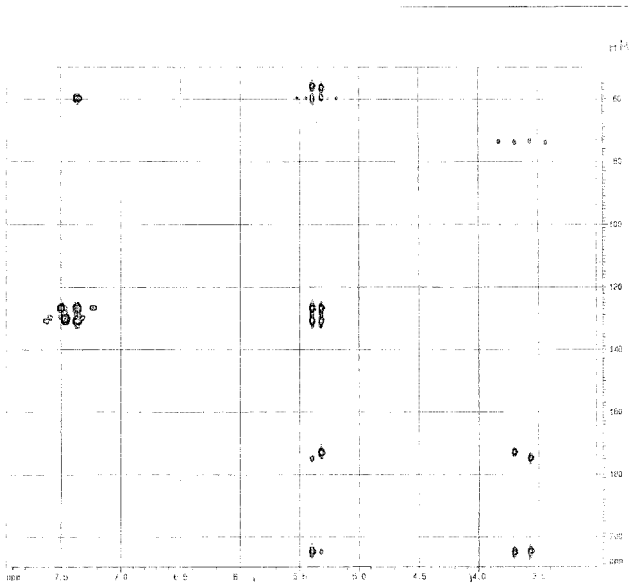

Figure 5. HMBC NMR of the mixture of products **2** and **3**. (For details, see Discussion and Experimental Section.)

Molecular modeling of **2** and **3** (R1 = phenyl) was carried out using Macromodel (version 5.0) software with the MM2 force field.[9−10] Preferred conformations were determined from the results of Monte Carlo conformer searches starting from previously minimized structures. One thousand Monte Carlo steps were performed yielding 4−6 unique conformations in the energy region of 0−10 kcal/mol. Results in Figure 6 indicate that both cis isomers **2** and **3** are energetically more stable than the trans counterpart **4** (not obtained) with about 8 kcal lower energy. This could be predicted as the cis isomers can both accommodate the bulky phenyl groups in a more energetically stable equatorial conformation; however, the trans isomers would always harbor one phenyl in the hindered axial conformation. These results are in correlation with the fact that the trans isomers were not obtained. From the other side, there is some energetic difference between both cis isomers with about 1 kcal in favor of isomer **2**. We cannot attribute this small energetic difference to a yield ratio favoring one of the isomers as the integration was done on the precipitated mixture and could not be performed on the crude solution as products precipitate rapidly from the beginning of the reaction (see Figure 6).

The feasibility of the reaction was demonstrated for benzaldehyde with yields ranging between 80 and 90%. The product precipitates directly form the reaction mixture, which might facilitate isolation in a parallel synthesis array.

The new scaffold contains a lactone, which can be further modified into substituted lactam, and a ketone which is suitable for further reduction or substitution. Overall, the new spiro bicyclic scaffold is highly versatile for obtaining second generation diversity libraries.[11]

After extensive bibliographical research we have found only four reports on one pot generation of spiro heterobicyclic systems, and all of them included cyclization of a preformed molecule[12] or condensation between two components.[13−15] Thus, this is the first report for a one pot generation of spiro heterobicyclic systems using a multi-component reaction of more than two components (pseudo-four in this case).

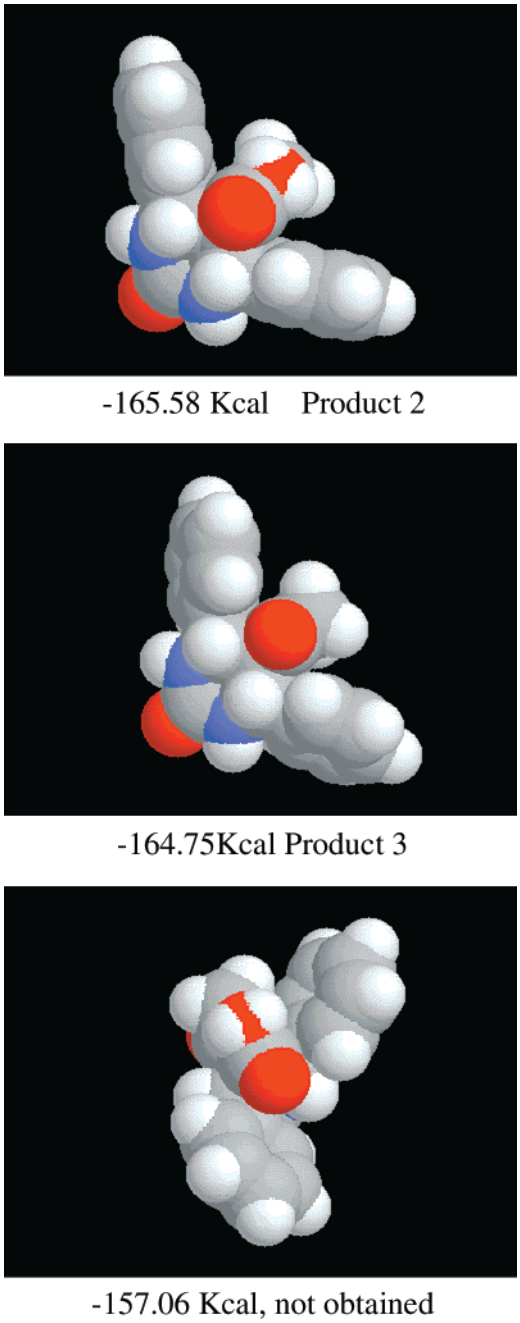

Figure 6. Molecular model and calculated energy levels of products **2** and **3** (upper panels) and a hypothetical trans isomer (lower panel).

Conclusions

The new spiro heterobicyclic scaffold is a significant contribution to the field of combinatorial chemistry. The originality of the scaffold allows a direct synthesis of novel diversity libraries for biological screening. Moreover, the presence of a lactone and a ketone in the scaffold permits the further generation of secondary libraries,[13] thus increasing the diversity of products. We are currently studying extensive series of different substituted ureas and aldehydes to generate more diverse libraries as well as the solid-phase application of this reaction. Additionally, in order to better understand and extend this novel multicomponent reaction, we are

studying kinetic, thermodynamic, and mechanistic aspects that will be published elsewhere.

Experimental Section

Materials and Methods. Reagents were purchased from Aldrich and used without further purification. All solvents were analytically pure grade and were used without further purification. **Analytical HPLC** were performed on a Waters Gradient System equipped with a Waters 717-Plus autosampler, a Waters 600 intelligent pump, and a Waters 996 photodiode array detector, and the system was piloted with Millenium software from Waters. Mobile phases were (A) H_2O (0.1% TFA) and (B) MeCN (0.08% TFA). Separation conditions were as follows: column C18 218TP54 from Vydac, gradient [A/B]: 3 min. [80/20], 3−25 [0/100]. 25−35 [0/100], flow = 1 mL/min.

Preparative separation of products **2** and **3** was performed using silica gel 60 (0.015−0.040 μm) from Merck using two different devices and separation conditions described in the Experimental Section bellow. NMR and MS were carried out at the Structural Analysis Department of Bar-Ilan University. ^{1}H NMR spectra was recorded on a Brucker DPX-300 and DMX-600 MHz spectrometers. Samples were dissolved in trifluoroacetic acid. Chemical shifts are in ppm relative to TMS internal standard. Mass spectra were carried out on a Finnigan 4020.

Structural Evaluation by Molecular Modeling Studies. Molecular modeling studies were carried out using Macromodel (version 5.0) software with the MM2 force field[9,10] in a Silicon Graphics station. Preferred conformations were determined from the results of Monte Carlo conformer searches starting from previously minimized structures. One thousand Monte Carlo steps were performed yielding four to six unique conformations in the energy region of 0−10 kcal/mol.

Synthesis of Products 2 and 3. A mixture of tetronic acid **1** (0.6 g, 0.01 mol), benzaldehyde (5.3 g, 0.05 mol), urea (0.6 g, 0.01 mol), and EtOH (15 mL) was stirred and heated at 85 °C under nitrogen. When all components were dissolved, 3 drops of concentrated HCl were added and a white solid began to precipitate immediately. After refluxing during 3 h, the solid was filtrated to yield 2.71 g (80%) of a mixture of isomers **2** and **3**. MS: 337 (MH^+). ^{1}H NMR product **2**: δ 3.57 (s, 1H), 5.4 (s, 2H), 7.46 (m, 5H); product **3**: δ 3.7 (s, 1H), 5.32 (s, 2H), 7.38 (m, 5H). ^{13}C NMR (75 MHz) product **2**: δ 204.53 (CO), 174.6 (COO), 158.88 (CONH), 73.87 (C), 59.63 (CH), 55.78 (CH_2), 130.8, 130.7, 129.57, 126.53 (C_6H_5); product **3**: δ 204.53 (CO), 172.76 (COO), 130.7, 130.64, 129.65, 126.53 (C_6H_5), 73.52 (C), 59.53 (CH), 56.19 (CH_2). HPLC: R_t = 17.24 min (product **2**), 17.54 min (product **3**).

For the isolation of product **2** a column of 35 × 4.5 cm from Aldrich was used with a mixture of $CHCl_3$:hexane:AcOH, 9:2.5:0.1, at a flow of 1 mL/min. Pure product **2** eluted between 74 and 100 min. MP: 205 °C. MS: 337 (MH^+). ^{1}H NMR (75 MHz): δ 3.57 (s, 1H), 5.4 (s, 2H), 7.46 (m, 5H). HPLC: R_t = 17.31 min. R_f: 0.2 ($CHCl_3$:hexane:AcOH, 9:2:0.1; three runs).

For isolation of product **3** a column of 45 × 2 cm from Buchi using a gradient former B-687 equipped with a chromatography pump B-688 from Buchi. The gradient conditions were the following A = hexane, B = $CHCl_3$:AcOH, 9:0.1. Flow: 8 mL/min. 0 min: from A/B = 100/0 to 95 min. A/B = 0/100, then 100% B for additional 150 min. The pure product **3** eluted between 121 and 148 min. MP: 200 °C, MS: 337 (MH^+). HPLC: R_t = 17.60 min. R_f: 0.27 ($CHCl_3$:hexane:AcOH, 9:2:0.1; three runs).

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