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Approach to the Library of 3-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones through a Three-Component Condensation

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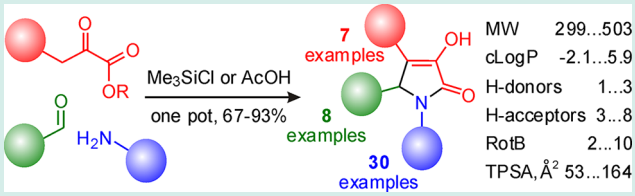
Supporting Information

ABSTRACT: A convenient procedure for the parallel synthesis of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones through a three-component condensation of active methylene compounds, aldehydes, and amines was developed. It was shown that the use of acetic acid as the reaction medium was suitable for the considerably reactive substrates with no additional functionalities. The substrates with low reactivity and those possessing carboxylic groups or additional basic centers required the use of DMF as the solvent and chlorotrimethylsilane as the reaction promoter was necessary. More than 3000 pyrrolones were synthesized by the developed procedure. To demonstrate the scope of the described approach 114 library representatives were fully characterized.

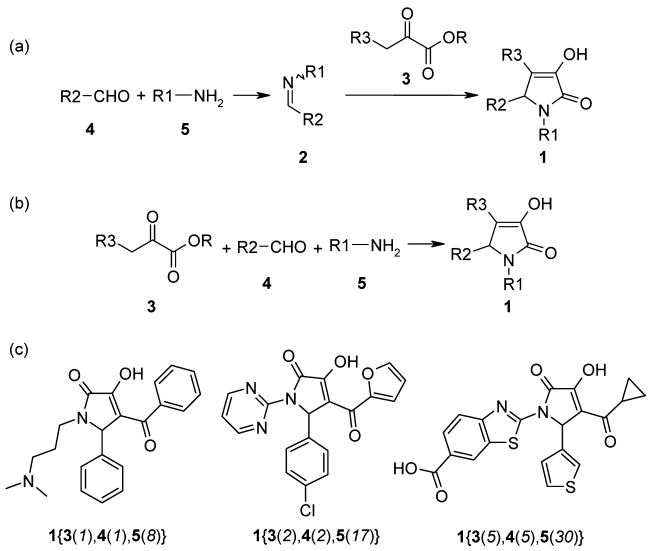


KEYWORDS: *multicomponent reaction, pyrrole, condensation, chlorotrimethylsilane, aldehyde, amine*

Adaptation of synthetic procedures to the requirements of combinatorial chemistry has always been a tremendous task to solve.[1] Multicomponent reactions (MCR)[2] represent a useful tool to the combinatorial chemistry tasks because of the high diversity of the compound libraries thus produced and one-pot procedures employed. Nevertheless, in many cases using a two-step reaction sequence, with the need to introduce reagents to affect the second step, is more effective because of the usually higher yields and a simplified isolation and purification of the products. The synthesis of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **1** represents an example of such a transformation. In most cases, pyrrolones **1** were obtained using a two-step procedure, that is, via the formation of imines **2** followed by their condensation with pyruvates **3** (Scheme 1), whereas only a limited number of examples of the pyrrolone syntheses by the one-pot three-component reaction of **3**, **4**, and **5** were reported in the literature.[3−8] The latter method was shown to be high-yielding with the most reactive substrates.[9,10] At the same time the use of substrates with low reactivity led to moderate or low yields of **1**.[11−14] Therefore the previously reported procedures for the one-pot three-component preparation of **1** need further improvement to become compatible with parallel synthesis conditions.

Compounds of the general formula **1** have been shown to possess a wide range of biological activities, that is, as peptide−protein interaction inhibitors,[4] HIV-1 integrase inhibitors,[5] vasopressin-2 receptor antagonists,[6] compounds with nootropic,[15] bacteriostatic, antiamnesic and antitumor,[7] antiflogistic,[8] antibacterial,[10,12,13,16] antiviral,[14,17] antiarthritic,[18] and antineoplastic[19] activity. Given the importance of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones (**1**) to medicinal chemistry and drug discovery, we have turned our attention to the development of a method for their preparation under parallel synthesis conditions. In connection with this, a three-

Scheme 1. Synthesis of 3-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones 1 (a) by the Two-Step Reaction Sequence and (b) by the One-Pot MCR and (c) Examples of the Products



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component reaction depicted in the Scheme 1 (**3** + **4** + **5**) would be the method of choice with all the advantages of MCR discussed above. Apart from the high efficiency, this method considers the possibility of introducing a variety of substituents to improve the physicochemical parameters of the compounds (that is, polar groups such as amino, carboxyl, or hetaryl), allowing for a lead-oriented approach to the library design.[20] On the basis of our previous experience with the use of chlorotrimethylsilane as a mild and efficient promoter for various condensation reactions of carbonyl compounds,[21] we proposed the similar conditions for the three-component reaction of the active methylene compounds **3**, aldehydes **4**, and amines **5**. Thus, DMF was used as the solvent and chlorotrimethylsilane as the condensation promoter. The reaction temperature and time were 100 °C and 2−8 h, respectively. In addition, the classical reaction conditions involving heating of the starting materials in acetic acid in at 100 °C for 2−8 h were also tested. We have found that in the case of pyruvates **3**(*1*−*9*), aldehydes **4**(*1*−*7*), and simple aliphatic amines or anilines **5**(*1*−*7*) (Figures 1−3), the use of

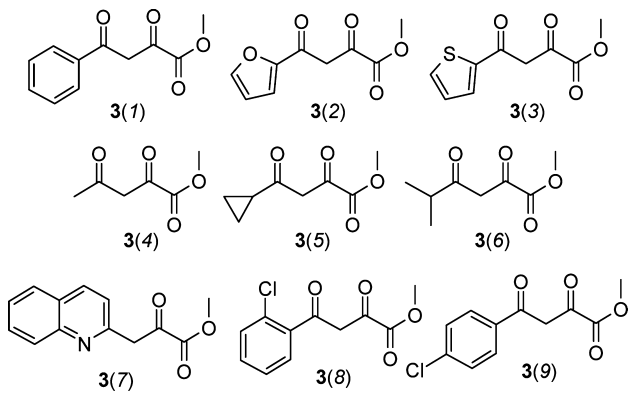

Figure 1. Pyruvates **3**(*1*−*9*) used in this work for the synthesis of pyrrolones **1**.

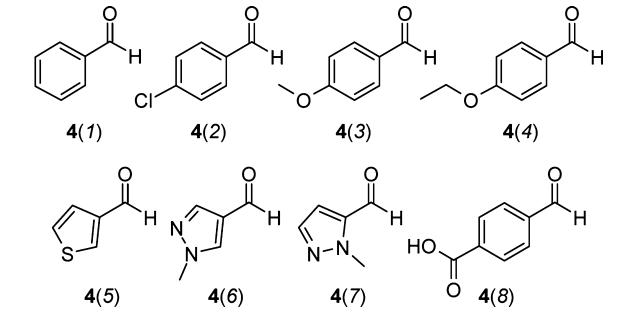

Figure 2. Aldehydes **4**(*1*−*8*) used in this work for the synthesis of pyrrolones **1**.

acetic acid as the reaction promoter was very efficient: the pyrrolones **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*1*−*7*)} were obtained in 73−87% yields (see Table S1 of the Supporting Information).

In the case of Me_3SiCl-promoted reactions, the yields of **1** were slightly lower (64−78%), possibly because of the high reactivity of the amines **5**(*1*−*7*), which led to considerable side reactions and complicated the purification of the products.

Nevertheless, the efficiency of the Me_3SiCl-promoted reactions was reversed in the case of amines **5**(*8*−*12*) possessing an additional basic center. The successful action of Me_3SiCl gave rise to pyrrolones **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*8*−*12*)} in 67−86% yields, whereas the preparation of these compounds in acetic acid showed lower yields of 57−71%. The decreased yields of **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*8*−*12*)} can be attributed to the formation of acetates which decreased the reactivity of the amines. It should be noted that Me_3SiCl was an effective reaction promoter in the case of amine **5**(*13*), presumably because of the dynamic protection of the additional secondary amine function. An attempt at the preparation of **5**(*13*) in acetic acid gave a complex mixture of products.

In the case of amines **5**(*14*−*16*) with moderate nucleophilicity, both Me_3SiCl and acetic acid were equally efficient, although prolonged reaction times were required to obtain the pyrrolones **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*14*−*16*)} in 81−91% yields. Me_3SiCl was the reaction promoter of choice for the least reactive heteroaromatic amines **5**(*17*−*27*), which gave the corresponding products **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*17*−*27*)} in 73−93% yields (vs 38−73% in the case of the reaction in acetic acid).

Acetic acid showed low efficiency as the reaction promoter in the case of amines **5**(*28*−*30*) possessing the carboxyl moiety. The formation of the desired products in less than 10% yield was detected by LC−MS analysis of the crude precipitates obtained after the aqueous workup of the reaction mixtures. On the contrary, Me_3SiCl was still useful for the reaction of **5**(*28*−*30*), and the corresponding pyrrolones **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*28*−*30*)} were isolated in 74−86% yields.

Notably, no significant influence of the structure of active methylene compounds **3**(*1*−*9*) and aldehyde component **4**(*1*−*7*) on the reaction outcome could be noticed. Yet again, Me_3SiCl was more effective as the reaction promoter than acetic acid in the case of carboxy-substituted aldehyde **4**(*8*). The influence of the structure of various aliphatic, (hetero)-aromatic and functionalized aldehydes on the outcome of Me_3SiCl-promoted condensations was extensively studied by us earlier; the results obtained herein are in accordance with our previous findings.[22] In particular, the method described in this work was not effective with nonbranched aliphatic aldehydes and ketones (as the carbonyl components of the reaction) due to their tendency to self-condense under the reaction conditions.

In conclusion, a convenient procedure for the parallel synthesis of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones through a three-component condensation involving active methylene compounds, aldehydes, and amines was developed. It was shown that the use acetic acid as the reaction medium would be efficient in the case of reactive substrates possessing no additional functionality. In the case of substrates with low reactivity (that is, heteroaromatic amines), or those possessing additional acidic or basic groups, Me_3SiCl-promoted reaction conditions were found to be more appropriate. The method was used to prepare more than 3000 compounds of which 114 were characterized and described in this paper. The predicted values of physicochemical properties for these library members are within the accepted limits for the large portion of the library **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*1*−*30*)} (Table 1, see also Supporting Information),[23] except the cut-offs proposed by Churcher et al.[20a] (Figure 4).

EXPERIMENTAL PROCEDURES

Solvents were purified according to the standard procedures. All the starting materials were purchased from Acros, Merck, Fluka, and Ukrorgsyntez. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical

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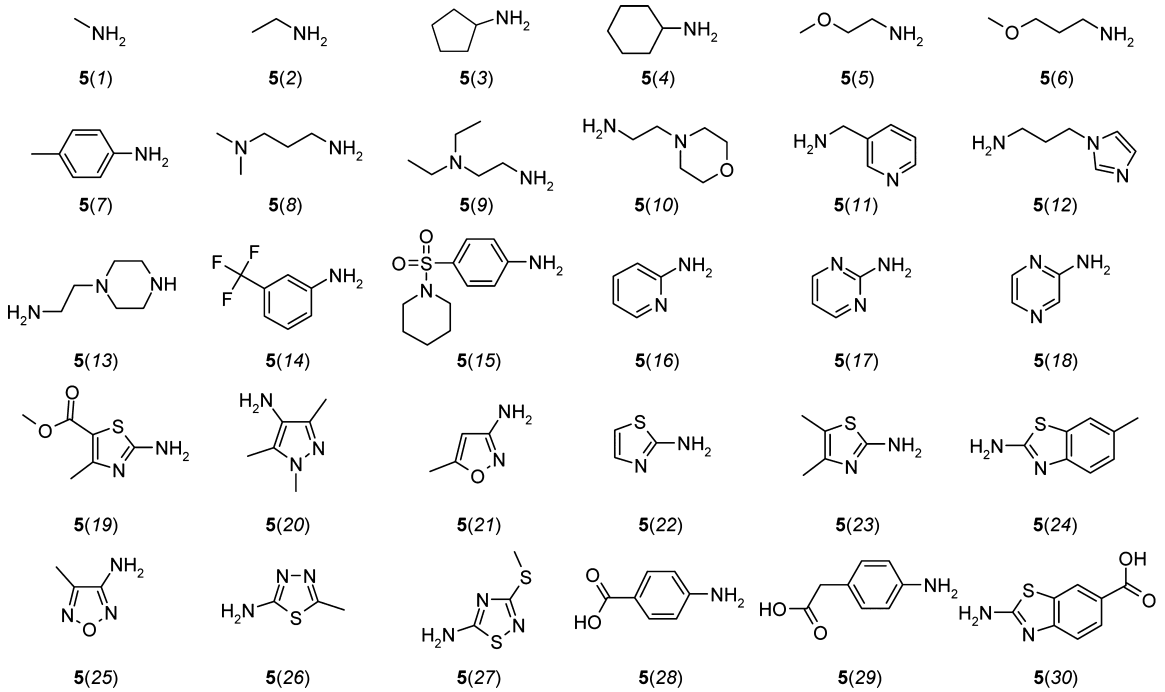

Figure 3. Amines **5**(*1*−*30*) used in this work for the synthesis of pyrrolones **1**.

Table 1. Predicted Values of Physicochemical Properties of 114 Library Members 1{3(*1*−*9*),4(*1*−*7*),5(*1*−*30*)}

entry	parameter	value range	average value
1	molecular weight (MW)	299.4−502.6	411.8
2	cLogP	−2.07−5.90	2.10
3	number of H-bond donors	1−3	1.1
4	number of H-bond acceptors	3−8	5.8
5	number of rotatable bonds	2−10	5.9
6	total polar surface area (TPSA), Å^2	53.4−164.3	95.8

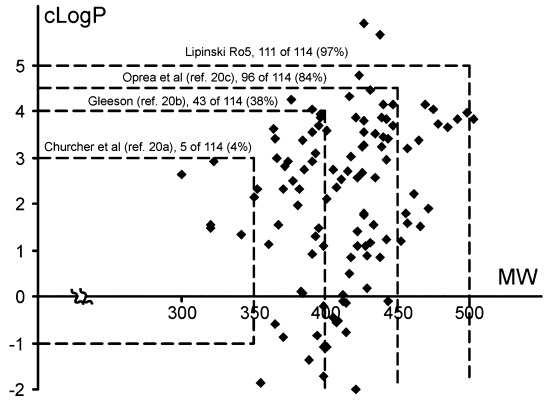

Figure 4. Physicochemical properties of 114 synthesized library members **1**{**3**(*1*−*9*),**4**(*1*−*7*),**5**(*1*−*30*)} shown in cLogP−MW plot.

TLC was performed using Polychrom Supporting Information F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. HPLC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University.

General Procedure for the Reaction of 3, 4, and 5. *Method A.* Pyruvate **3** (1 mmol), aldehyde **4** (1 mmol), and amine **5** (1 mmol) were placed in a 15 mL screw cap vial and dissolved in DMF (1−2 mL). Chlorotrimethylsilane (544 mg, 5 mmol) was added portionwise to the solution. The tube was thoroughly sealed and heated on a steam bath for 2−8 h. After cooling, the flask was opened (***Caution!*** *Excessive pressure inside*), and H_2O (10 mL) was added portionwise to the solution. The suspension formed was sonicated at 20 °C in an ultrasonic bath for 2 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH (1−2 mL) or EtOH (1−2 mL) to yield the targeted library member **1**.

Method B. Pyruvate **3** (1 mmol), aldehyde **4** (1 mmol), and amine **5** (1 mmol) were placed in a 15 mL screw cap vial and dissolved in AcOH (1−2 mL). The reaction mixture was refluxed for 2−8 h. After cooling, the flask was opened, and H_2O (10 mL) was added portion-wise to the solution. The suspension formed was sonicated at 20 °C in an ultrasonic bath for 2 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH (1−2 mL) or EtOH (1−2 mL) to yield the targeted library member **1**.

■ ASSOCIATED CONTENT

Supporting Information

Table S1, distributions of physicochemical properties for 114 library members, cLogP−MW plot for the 3615 library members, compound characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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