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Biginelli-like reaction with dialkyl acetone-1,3-dicarboxylates: a remarkable case of steric control

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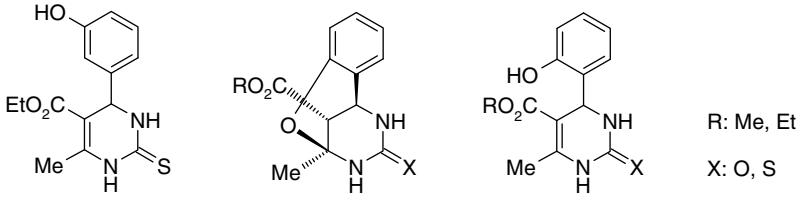
Abstract

A Biginelli-type condensation is described using dialkyl acetone-1,3-dicarboxylates as active methylene compounds for the preparation of monastrol analogues. Unexpectedly, the reaction with salicylaldehyde formed two different products depending on the ester alkyl group. This product dichotomy was found to be caused by the steric effects exerted by the alcohol terminus of the ester group in the active methylene component. Previous controversial results as to the structure of the Biginelli product **3** are also discussed.

Monastrol (±)-**1**, ethyl 6-methyl-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, is a recently highlighted Biginelli compound,[1] which showed promise in a new strategic approach to cancer research.[2] Compound **1** has been found[1] to affect the function of mitotic kinesin Eg5, a motor protein responsible for spindle bipolarity.[3] Thus, kinesin spindle protein represents an attractive target for biochemical studies because human Eg5 inhibitors induce cell death via apoptosis.[4] With regard to the pharmacological profile and other promising medicinal applications of similarly functionalized 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones, their synthesis via the Biginelli reaction has been thoroughly studied.[5] Numerous modifications and improved procedures for the cyclocondensation of alkyl acetoacetate with aldehydes and urea or thiourea have been developed.[5] We reported[6] that the three-component heterocyclization with salicylaldehyde produced oxygen-bridged pyrimidine derivatives, for example, 2,6-methano-4-oxo- and 4-thioxo-3,4,5,6-tetrahydro-2*H*-[1,3,5]-benzoxadiazocines (**2**) rather than the previously reported[7] 4-(2-hydroxyphenyl)pyrimidines (**3**). However, oxygen-bridged pyrimidine structures were not discussed in several recent reports.[8–11] but were supported by others.[12–14] Herein, we present an unexpected product dichotomy in the Biginelli-like condensation of 2-hydroxybenzaldehyde with urea or thiourea and dimethyl or diethyl acetone-1,3-dicarboxylate, respectively, as active methylene components.



1 **2** **3**

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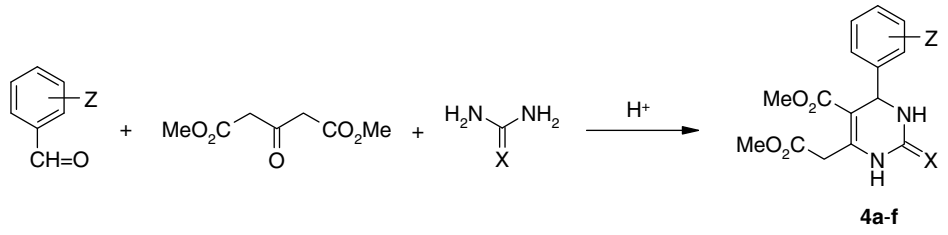
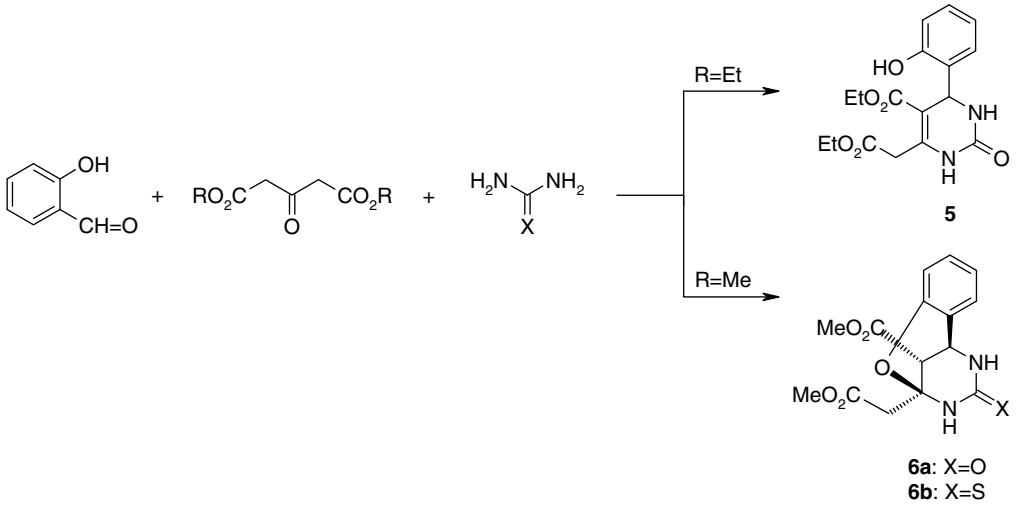


a: X=O **d**: X=S Z=H; **b**: X=O **e**: X=S Z=3-OH; **c**: X=O **f**: X=S Z= 3,4-$(OMe)_2$

Scheme 1.

In the course of our work on the synthesis of monastrol analogues **4a**–**f**, starting from dimethyl 3-oxopentanedioate (Ref. 15, Scheme 1), a report appeared[16] in which the authors described a preparation of closely related diethyl esters including a congener **5** possessing the 4-(2-hydroxyphenyl) moiety (Scheme 2). Considering the possible formation of benzoxadiazocines **2**, we decided to verify the structure of the uncyclized molecule **5**. A careful repeat of the original experiment[16] (solvent free, 80 °C, 3 h, 2 mol % TsOH as an acid catalyst) and the subsequent comparison of the reported and our NMR spectra clearly confirmed the published dihydropyrimidine structure **5** (Scheme 2). In contrast, when the condensation of salicylaldehyde with dimethyl acetone-1,3-dicarboxylate was performed under the above-described conditions a different type of product resulted. Based on the spectroscopic data,[17] the product obtained from the methyl ester was the conformationally restricted tricycle **6a** (Scheme 2). Intramolecular Michael addition of the phenolic hydroxyl group has occurred as indicated by the ^{1}H NMR spectrum of the product displaying an AB quartet of the diastereotopic methylene protons of the 6-methoxycarbonylmethyl substituent. In addition, the ^{13}C NMR signal for the *N*,*O*-acetal sp^3 carbon at δ 80 provides convincing evidence of cyclization as well. The analogous reaction with thiourea proceeded similarly to yield 4-thioxo derivative **6b** (Ref. 17, Scheme 2). Both cyclizations were found to be diastereoselective proceeding with exclusive formation of one isomer as evidenced by NMR analysis of the reaction mixture.

In light of the above findings, we proceeded to explore the rationale for the dichotomy in the reactivity of dimethyl and diethyl acetone-1,3-dicarboxylates. Considering the mechanism of the Biginelli condensation which leads to the oxygen-bridged pyrimidines **2**, there is no doubt that electronic effects do not play a significant role in affecting the reaction course. Consequently, steric control seems to be the key factor in determining the products of the condensation. The formation of the oxygen bridge is likely to depend on the effective distance between the phenol *ortho*-hydroxyl and the pyrimidine C-6 atom. According to molecular mechanics calculations,[18] the optimum proximity of these centres was estimated to be 3.20–3.51 Å. Apparently, such an arrangement results from a suitable molecular conformation. Inspection of Dreiding models indicates that the C-6 position is considerably hindered by the adjacent ethoxycarbonyl moiety, as compared to the less bulkier COOMe group, while rotating about the O=C(OR)–CH_2 single bond. In contrast to the methyl acetate unit, the 6-CH_2COOEt substituent pushes the *ortho*-hydroxyl away from its bonding contact. As a result, the final ring closure via Michael addition is predicted to occur only in the case of the dimethyl ester.



Scheme 2.

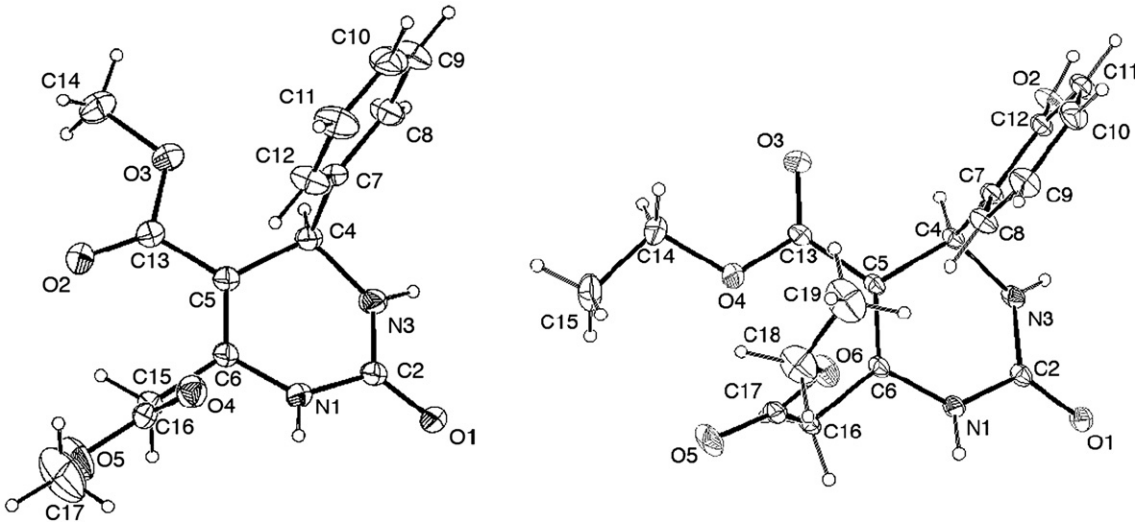


Fig. 1. ORTEP views of tetrahydropyrimidines **4a** (left) and **5** (right).

Since we were able to grow single crystals of two model compounds, **4a** and **5**, we determined X-ray structures to compare their molecular conformations.[19] ORTEP drawings (Fig. 1) reveal evidently different spatial arrangement of the ester groups between these tetrahydropyrimidines in both the positions 5 and 6.

In order to clarify the previously reported structures **3**,[8–11] we re-examined some of the reported catalysts,[9] namely $NiCl_2{\cdot}6H_2O$ and $FeCl_3{\cdot}6H_2O$, that were used in the Biginelli reaction with salicylaldehyde. As seen from NMR spectra, the product prepared according to the published protocol[9] was not pyrimidine **3** but benzoxadiazocine **2**. Apparently, the discrepancy between our and some of the literature results originates from the use of Folkers's[7] structure **3** dating back to 1932, which has been disproved by our detailed spectroscopic analysis.

In summary, we have elucidated the structures of two heterocyclic products formed in the Biginelli-like reaction of salicylaldehyde with urea/thiourea and dimethyl or diethyl acetone-1,3-dicarboxylate. The results have shown that the steric effect of the alcohol ester group is the main determinant for the final cyclization step. The Biginelli dihydropyrimidines prepared here represent attractive monastrol analogues which are under in vitro and in vivo chemical genetic studies. Moreover, the molecular conformation of the target dihydropyrimidine dimethyl esters conform to the Triggle dihydropyridine receptor binding model,[20] and thus the compounds could become the suitable candidates for calcium channel modulatory activity trials.

Acknowledgements

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15. Although the condensation proceeds in refluxing ethanol under HCl, *p*-TsOH or H_2NSO_3H catalysis, the reaction time was too long (>30 h), thus solvent free conditions and the corresponding protocol as described in Ref. 16 were employed. All the compounds reported here gave satisfactory CHN microanalyses. Characteristic data for **4a**: Mp 180–182 °C (EtOH), isolated yield 39%; IR (KBr) ν_{max} 3409

(NH), 1729 (COO), 1702 (COO+NCON), 1650 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.48 (s, 3H, OMe 5-ester), 3.65 (s, 3H, OMe ester), 3.68 (d, 1H, $J = 16.8$ Hz, CH_2), 3.82 (d, 1H, $J = 16.8$ Hz, CH_2), 5.17 (d, 1H, $J = 3.3$ Hz, H-4), 7.22–7.29 (m, 1H, H_{Ar}), 7.30–7.37 (m, 4H, H_{Ar}), 7.84 (br s, 1H, NH-3), 9.32 (s, 1H, NH-1); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 36.8 (CH_2), 51.0 (OMe 5-ester), 51.9 (OMe ester), 53.8 (CH-4), 100.6 (C-5), 126.5 (CH-2′ and 6′), 127.5 (CH-4′), 128.5 (CH-3′ and 5′), 144.2 (C-1′), 145.1 (C-6), 152.0 (NCON), 165.4 (COO 5-ester), 169.2 (COO ester). Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.31): C, 59.21; H, 5.30; N, 9.21. Found: C, 59.32; H, 5.33; N, 9.09. Product **4b**: Mp 154–156 °C (EtOH), yield 36%; Product **4c**: Mp 189–190 °C (EtOH), yield 48%; Product **4d**: Mp 175–177 °C (MeOH), yield 35%; Product **4e**: Mp 185–187 °C (MeOH); Product **4f**: Mp 186–188 °C (MeOH), yield 44%.

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17. Methyl (2*R**,6*R**,11*S**)-2-methoxycarbonylmethyl-4-oxo-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxylate (**6a**): Mp 214–216 °C (MeOH), yield 63%; IR (KBr) ν_{max} 3201 (NH), 1746 (COO), 1731 (COO), 1678 (NCON) cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz) δ 3.13 (d, 1H, $J = 15.9$ Hz, 6-CH_ACO_2), 3.43 (d, 1H, $J = 15.9$ Hz, 6-CH_BCO_2), 3.62 (s, 3H, OMe ester), 3.70 (m, 1H, H-11), 3.72 (s, 3H, OMe ester-11), 4.57 (dd, 1H, $J = 4.8$ and 3.0 Hz, H-6), 6.80 (d, 1H, $J = 7.8$ Hz, H-10), 6.95 (dt, 1H, $J = 7.5$ and 1.4 Hz, H-8), 7.20 (dt, 1H, $J = 7.3$ and 1.5 Hz, H-9), 7.21 (d, 1H, $J = 7.7$ Hz, H-7), 7.43 (d, 1H, $J = 4.2$ Hz, NH-5), 7.66 (br s, 1H, NH-3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 40.4 (CH_2), 41.6 (CH-11), 47.4 (CH-6), 51.7 (OMe ester), 52.1 (OMe ester-11), 83.0 (C-2), 116.8 (CH-10), 121.1 (CH-8), 125.1 (C-6a), 128.8 (CH-7), 129.5 (CH-9), 150.1 (C-10a), 154.2 (CO), 168.9 (COO ester-11), 169.2 (COO ester); a four-bond interaction of W type between NH-5 and H-11 found in the HMBC spectrum together with a weaker cross-peak between NH-3 and H-11 in the COSY spectrum proved clearly an axial orientation of the 11-COOMe group. **6b**: Mp 198–200 °C (MeOH), yield 21%; IR (KBr) ν_{max} 3398, 3356 (NH), 1751 (COO), 1737 (COO) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.36 (t, 2H, $J = 17.0$ Hz, CH_2), 3.62 (s, 3H, OMe ester), 3.72 (s, 3H, OMe ester-11), 3.76 (br s, 1H, H-11), 4.69 (dd, 1H, $J = 4.8$ and 2.7 Hz, H-6), 6.84 (d, 1H, $J = 7.8$ Hz, H-10), 6.98 (t, 1H, $J = 7.4$ Hz, H-8), 7.22 (d, 1H, $J = 7.2$ Hz, H-7), 7.26 (t, 1H, $J = 8.0$ Hz, H-9), 9.18 (br s, 1H, NH- 3), 9.34 (d, 1H, $J = 4.2$ Hz, NH-5); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 39.7 (CH_2), 40.0 (CH-11), 47.9 (CH-6), 51.8 (OMe ester), 52.4 (OMe ester-11), 81.3 (C-2), 116.6 (CH-10), 121.4 (CH-8), 123.4 (C-6a), 129.0 (CH-7), 129.9 (C-9), 150.0 (C-10a), 168.3 (COO ester-11), 169.1 (COO ester), 176.6 (C=S); EI MS (*m*/*z*) 336 (M^+).
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19. Crystallographic data (excluding structures factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 679852 for **4a** and 679853 for **5**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
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