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Novel efficient synthesis of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones

Luís M. T. Frija,[a] Igor V. Khmelinskii[b] and M. Lurdes S. Cristiano[a,*]

[a]*CIQC, Departamento de Química e Bioquímica, F.C.T. Universidade do Algarve, Campus de Gambelas, 8005-039 Faro, Portugal*
[b]*CMQA, Departamento de Química e Bioquímica, F.C.T. Universidade do Algarve, Campus de Gambelas, 8005-039 Faro, Portugal*

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Abstract—A new attractive and convenient strategy for the synthesis of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones is described. Photolysis ($\lambda = 254$ nm) of 4-allyl-tetrazolones in alcoholic solutions produces the corresponding pyrimidinones as the sole product in nearly quantitative yields, with simultaneous extrusion of molecular nitrogen. Work-up procedures consist in the simple evaporation of the solvent under reduced pressure, in mild conditions. Heats of reaction for the photocleavage process of 4-allyltetrazolones were calculated, indicating high stability of the resulting products.

3,4-Dihydro-pyrimidin-2(1*H*)-ones are compounds that have drawn widespread attention, due to their medical applications.[1] For instance, dihydropyrimidinone derivatives have been screened for antihypertension,[2] antibacterial,[3] anti-inflammatory[4] and anticarcinogenic[5] activities or as selective α_{1a}-andrenergic receptor antagonists.[6] The described synthetic routes to these compounds generally involve multi-step transformations that are essentially based on the Biginelli condensation methodology.[7–9] The present paper reports a new synthetic route to 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones **5** from 5-allyloxy-1-aryltetrazoles **3** in nearly quantitative yields. Interestingly, compounds **5** constitute a novel structural class of pyrimidinones, with no published description or synthesis to the best of our knowledge.

In previous contributions, we have reported results of our investigation on the structure and reactivity of 5-allyloxytetrazoles **3** (Scheme 1). These compounds can be obtained from allylic alcohols **2** through reaction with commercially available 5-chloro-1-phenyltetrazole **1**,[10] in high yields (around 80%).[11] A wide range of these compounds can be synthesised, by using different allylic alcohols and also by the introduction of substituents on the phenyl ring attached to the tetrazolyl system. Allyl tetrazolyl ethers **3** can be used as intermediates for selective conversion of allylic alcohols into the corresponding alkenes through transfer hydrogenolysis catalysed by Pd/C.[12] Also, when heated neat or in solution, these ethers can be quantitatively converted to the corresponding 4-allyltetrazolones **4** via a concerted Claisen-type isomerisation, affording exclusively the [3,3′] isomers.[11,13,14]

It has been observed that photolysis of a range of tetrazolyl derivatives, in solution or isolated in inert cryogenic matrices, may proceed through several photochemical processes, all of them involving cleavage of the tetrazole ring.[15–18] Several photoproducts are observed, with their chemical nature and relative ratio depending on their thermochemical stability and the structure of the starting tetrazole. One of the reaction channels for photodegradation is the initial photocleavage of the formally single bonds N1–N2 and N3–N4, with loss of N_2. Sustained by this knowledge and by our experience concerning the synthesis and reactivity of 5-allyloxytetrazoles, we have formulated the possibility of formation of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones **5** from 4-allyl-tetrazolones **4** by photolysis, via molecular nitrogen extrusion followed by ring closure.

Optimised experimental conditions for the photochemical conversion of 4-allyltetrazolones **4a**–**c**[19–21] (Scheme 1)

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* Corresponding author. Tel.: +351 289800100x7642; fax: +351 289819403; e-mail: mcristi@ualg.pt

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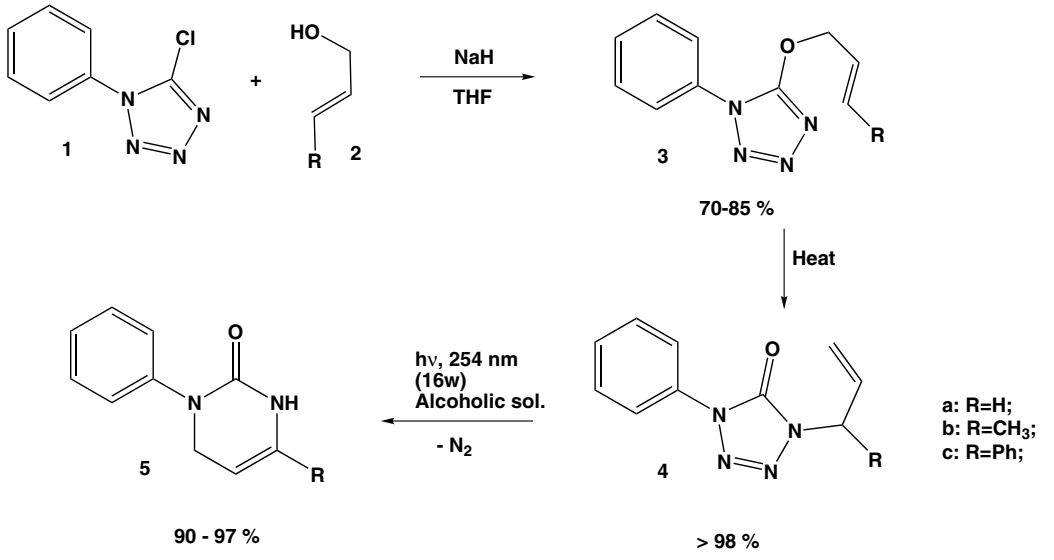


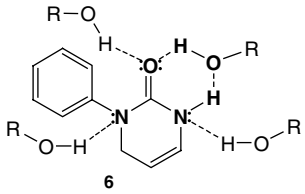
Scheme 1.

into 3,4-dihydro-6-substituted-3-phenylpyrimidin-2- (1*H*)-ones **5a**–**c**,[22–24] are now presented and discussed. Solutions of the 4-allyl-tetrazolones **4a**–**c** were irradiated in cyclohexane, carbon tetrachloride, acetonitrile, methanol, ethanol, 1-propanol and 1-hexanol. Irradiations ($\lambda = 254$ nm, 16 W low-pressure Hg lamp) were conducted using a merry-go-round and an immersion-well photochemical reactor (Applied Photophysics), placed at a distance of 5 cm from the lamp and immersed in water (25 °C) for cooling. Gas evolution from the solution was observed, corresponding to the photoeliminated molecular nitrogen.

Photolysis of 4-allyl-tetrazolones **4a**–**c** in cyclohexane, carbon tetrachloride and acetonitrile, leads to the formation of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones **5a**–**c** as sole primary photoproducts. However, it was observed that in these solvents, the photoproducts **5a**–**c** are photochemically unstable, undergoing a rapid decomposition to afford a mixture of secondary photoproducts identified as aniline, phenyl-, and allyl-isocyanates. Thus, it was never possible to obtain the required pyrimidinones as sole products when irradiations were performed in cyclohexane, carbon tetrachloride or acetonitrile.

Photolysis of the same tetrazolones **4a**–**c** in the protic solvents methanol, ethanol, 1-propanol or 1-hexanol also led to formation of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones **5a**–**c** as the sole primary photoproducts. However, in these solvents, pyrimidinones **5a**–**c** remained photostable even after extended periods of irradiation and no secondary photoproducts were ever detected throughout the exposure. The only by-product produced in these reactions is N_2, which is spontaneously eliminated from the reaction mixture. To our knowledge, this method has not been described previously and provides a valid access to a range of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones. The products are formed in nearly quantitative yields and their isolation is carried out by simple evaporation of the solvent under reduced pressure in mild conditions. The isolated dihydropyrimidinones can be stored as highly stable compounds. In our experiments, the amounts of 4-allyltetrazolone used varied between 100 and 300 mg. However, we believe that this methodology can easily be scaled up (>5 g). The introduction of substituents on the allylic part (e.g., phenyl in **4c**) only affects the time required for complete conversion (around 5 h for **4c**, as opposed to 3 h for compound **4a**). Thus, we consider that the methodology can be applied to a wider range of 4-allyl-1-substituted tetrazolones, allowing for the introduction of chemical diversity.

A probable explanation for the photostability exhibited by these compounds in alcoholic solutions, as opposed to cyclohexane, acetonitrile and carbon tetrachloride, is based on an efficient solvation through strong association between pyrimidinones **5a**–**c** and solvent molecules. Considering that the alcohols used can form relatively strong hydrogen bonds, we think that the stabilisation can be attributed to these phenomena, since pyrimidinones **5a**–**c** bear several putative atoms capable of forming hydrogen bonds with solvent molecules, as depicted in structure **6**. Product solvation would then be very efficient, through stable 'cages' enclosing the pyrimidinone molecules and preventing their photodecomposition. The influence of these *cage effects* is also related to the kinetic energy of the primary photoproducts and to the viscosity of the solvent, affecting the photolysis quantum yields. In the alcoholic solutions, the pyrimidinones have more difficulty in forming molecular fragments upon excitation due to the 'solvent cage', this effect increasing with the increase in alcohol viscosity. Also, the absorbed energy is more efficiently dissipated though the solvated complex, preventing relaxation through other pathways leading to photocleavage.



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Analysis of ^{1}H NMR spectra for compound **5b** was obtained in deuterated chloroform, acetonitrile and methanol. In $CDCl_3$ and CD_3OD, all protons connected to carbon atoms show a similar chemical shift. In CD_3CN, the resonances for the same protons are shifted downfield by 0.25–0.35 ppm. The signal due to the resonance of the proton connected to the nitrogen (N–H) appears at 10.2 and 9.1 ppm in $CDCl_3$ and CD_3CN, respectively, and is not observed in methanol.

In order to facilitate the mechanistic interpretation of the photocleavage, semi-empirical molecular orbital calculations were performed, using the PM-3 Hamiltonian[25] provided in the MOPAC 97 program.[26] The proposed reaction pathways for the formation of 3,4-dihydro-3-phenylpyrimidin-2(1*H*)-one **5a** from **4a** are presented in Figure 1. Considering N_2 elimination, the increase in the N1–N2 and N3–N4 bond lengths in tetrazolone **4a** was followed, until the stationary point was obtained. The geometry at this point was optimised by the eigenvector method and led to the transition structure (**TS1**). Rotation of the allylic chain in **TS1** and N_2 exclusion leads to a biradicalar complex (**BC1**) with the terminal carbon of the allylic chain (C1) very distant from N1 (4.72 Å). Subsequent reaction coordinate calculations considering that C1 approaches N1 provided a biradicalar complex (**BC2**) thermodynamically more stable by 19.1 kcal/mol. The formation of pyrimidinone **5a** from **BC2** ensues through 1,2-migration of hydrogen and formation of a new C1–N1 single bond, in an exothermic process. Similarly, reaction coordinates for the formation of compounds **5b–c** were obtained. Calculated heats of formation for tetrazolones **4b–c** (79.6 and 111.9 kcal/mol) are also substantially higher than those calculated for the corresponding photoproducts **5b–c** (−4.9 and 29.2 kcal/mol). Thus, based on the results of these semi-empirical calculations, we can conclude that the pyrimidinones **5** are thermodynamically more stable than the corresponding starting tetrazolones **4**.

In summary, we have successfully synthesised 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones **5a–c** from 4-allyl-tetrazolones **4a–c** through photolysis, in excellent yields, providing an alternative synthetic

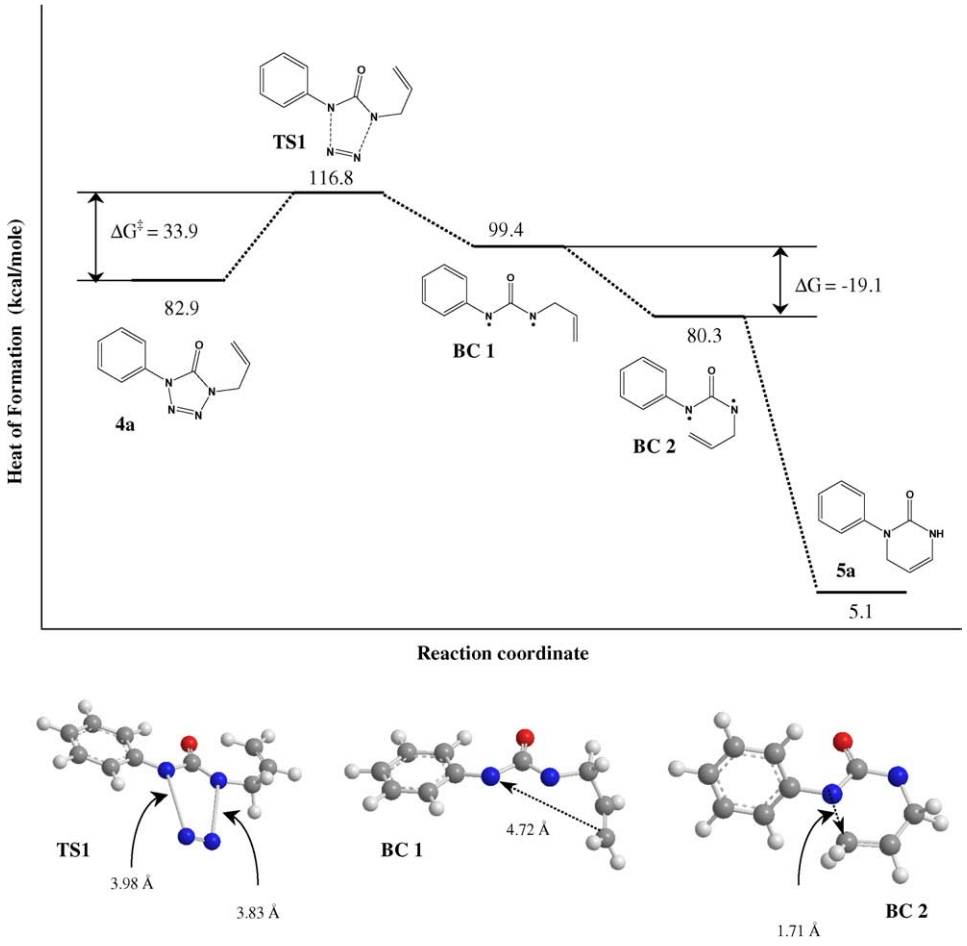

Figure 1. Energy profile for the formation of 3,4-dihydro-3-phenylpyrimidin-2(1*H*)-one **5a**. MOPAC (PM-3) optimised structures.

methodology to this class of compounds. Further investigations are in progress.

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19. 1-Phenyl-4-(prop-2-enyl) tetrazol-5-one **4a** from 1-phenyl-5-(prop-2-enyloxy) tetrazole **3a** (1.00 g; 4.90 mmol) heated neat at 150 °C for 3 h. ^{1}H NMR ($CDCl_3$): δ 4.65 (2H, d, J 5.7), 5.30–5.50 (2H, m), 5.90–6.10 (1H, m), 7.40–7.60 (3H, m), 8.00 (2H, d, J 6.86); $\nu_{max.}$: 1729 (C=O), 1598, 1504, 1388 and 757 cm^{-1}; MS (EI), m/z 202 [M]$^+$. Found: C, 59.8; H, 5.2; N, 28.1%. Calcd for $C_{10}H_{10}N_4O$: C, 59.4; H, 5.0; N, 27.7%.
20. 4-(1-Methylprop-2-enyl)-tetrazol-5-one **4b** from 1-phenyl-5-[(*E*)-but-2-enyloxy]tetrazole **3b**, 150 °C, 2 h. ^{1}H NMR ($CDCl_3$): δ 1.65 (3H, d, J 5.7), 4.90–5.10 (1H, m), 5.22–5.4 (2H, m), 6.0–6.2 (1H, m), 7.30–7.55 (3H, m), 7.95 (2H, d, J 8.6); $\nu_{max.}$: 1729 (C=O), 1599, 1504, 1382 and 757 cm^{-1}; MS (EI), m/z 216 [M]$^+$. Found: C, 61.0; H, 5.6; N, 26.1%. Calcd for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.6; N, 25.9%.
21. 1-Phenyl-4-(1-phenylprop-2-enyl)-tetrazol-5-one **4c** from 1-phenyl-5-[(*E*)-3-phenylprop-2-enyloxy] tetrazole **3c**, 100 °C, 2 h. ^{1}H NMR ($CDCl_3$): δ 5.28–5.52 (2H, m), 6.00 (1H, d, J 5.7), 6.36–6.55 (1H, m), 7.30–7.50 (7H, m), 7.95 (2H, d, J 8.6); $\nu_{max.}$: 1729 (C=O), 1598, 1504, 1382 and 756 cm^{-1}; MS (EI), m/z 278 [M]$^+$. Found: C, 68.8; H, 5.0; N, 20.4%. Calcd for $C_{16}H_{14}N_4O$: C, 69.1; H, 5.1; N, 20.1%.
22. 3,4-Dihydro-3-phenylpyrimidin-2(1*H*)-one **5a** from **4a** (0.10 g; 0.49 mmol) irradiated in methanol (50 mL), 3 h. The solvent was evaporated under reduced pressure at room temperature to give **5a**, 92% isolated yield. ^{1}H NMR ($CDCl_3$): δ 4.65–4.68 (2H, d), 5.25–5.50 (1H, m), 7.12–7.2 (1H, m), 7.37–7.43 (2H, m), 7.50–7.57 (2H, t), 10.35 (1H, s); $\nu_{max.}$: 3212 (NH), 3054, 1693 (C=O), 1590, 1566, 1496, 1368, 1230, 1059, 756 cm^{-1}; MS (EI), m/z 175 [M+H]$^+$.
23. 3,4-Dihydro-6-methyl-3-phenylpyrimidin-2(1*H*)-one **5b** from **4b**, in methanol, irradiated 3.5 h, 97% isolated yield. ^{1}H NMR ($CDCl_3$): δ 1.58–1.62 (2H, s), 3.75–3.78 (2H, d), 5.22–5.30 (1H, m), 6.15–6.25 (1H, m), 7.05–7.17 (2H, m), 7.25–7.42 (2H, m), 10.20 (1H, s); $\nu_{max.}$: 3284 (NH), 3085, 1681 (C=O), 1598, 1548, 1484, 1446, 1378, 1230, 1068, 755 cm^{-1}; MS (EI), m/z 189 [M+H]$^+$; Acc. Mass (CI): found = 189.10299, calcd for $C_{11}H_{13}N_2O$: 189.10280.
24. 3,4-Dihydro-3,6-diphenylpyrimidin-2(1*H*)-one **5c** from **4c**, in methanol, irradiated 5 h, 90% isolated yield. ^{1}H NMR ($CDCl_3$): δ 3.76–3.78 (2H, d), 5.42–5.48, (1H, m), 6.30–6.45 (1H, m), 6.70–6.75 (1H, m), 6.85–7.05 (2H, m), 7.10–7.35 (6H, m), 9.90 (1H, s); $\nu_{max.}$: 3220 (NH), 3066, 1701 (C=O), 1581, 1543, 1422, 1345, 1226, 1066, 756 cm^{-1}; MS (EI), m/z 251 [M+H]$^+$; Acc. mass (CI): found = 251.11809, calcd for $C_{16}H_{15}N_2O$: 251.11844.
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