

## Microwave-promoted reaction of *N*-(alk-1-enyl)chloroacetamides with sodium azide unexpectedly yields 1*H*-imidazol-5(4*H*)-ones

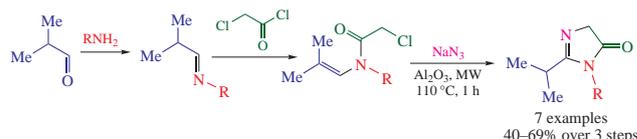
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DOI: 10.1016/j.mencom.2017.01.031

A novel method to prepare biologically relevant 1*H*-imidazol-5(4*H*)-ones from aliphatic amines, isobutyraldehyde, chloroacetyl chloride and sodium azide under microwave irradiation has been developed.

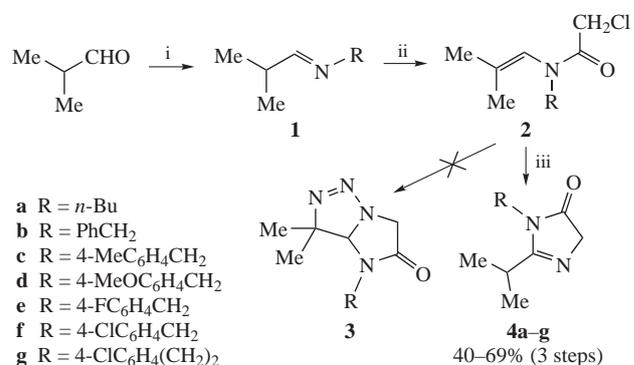


Multicomponent chemistry facilitates the design of compound arrays as it directly links the molecular periphery to a specific choice of mutually reactive reagents.<sup>1</sup> The resulting products can already contain a requisite scaffold determined by a particular multicomponent reaction (MCR) employed (*e.g.*, the Ugi diamides,<sup>2</sup> the Biginelli dihydropyrimidines,<sup>3</sup> the Hantzsch pyridines,<sup>4</sup> the Castagnoli–Cushman lactams,<sup>5</sup> *etc.*) or they further modified, as diversely substituted building blocks, *via* the final scaffold-defining post-MCR transformation.<sup>6</sup> The power of using pre-mediated post-MCR chemical events in generating broad skeletal diversity has been amply unveiled for the Ugi isocyanide-based multicomponent reaction.<sup>7</sup> In our scaffold-oriented research program, we have been interested in applying a similar strategy toward other MCRs<sup>8</sup> and recently, turned our attention to the reaction of acylating agents (acyl chlorides or carboxylic acid anhydrides) with imines containing a proton in the  $\alpha$ -position ( $\alpha$ -C–H imines) that is known<sup>9–13</sup> to furnish enamides. In particular, we have shown that the latter can be employed directly as building blocks for 1,3-dipolar cycloaddition of nitrile oxides to afford, with a high degree of atom economy, 4,5-dihydroisoxazoles containing four elements of diversity.<sup>14</sup> In the present study, we sought to investigate an intramolecular 1,3-dipolar cycloaddition between enamide and an appropriately positioned alkyl azide moiety.<sup>15</sup> This has led to an unexpected, yet practically sound and mechanistically intriguing outcome which we report herein.

Isobutyraldehyde was reacted with a series of alkylamines in the presence of  $\text{MgSO}_4$  as dehydrating agent to give imines **1**. The latter, without further purification, were acylated with chloroacetylchloride to give enamides **2**, which, in turn, were reacted with sodium azide under microwave irradiation in the presence of alumina as an HCl scavenger. The microwave-assisted step was expected to furnish, after chloride-to-azide displacement, 3a,4-dihydro-3*H*-imidazo[1,2-*c*][1,2,3]triazol-5(6*H*)-one products of Huisgen-type 1,3-dipolar cycloaddition reaction **3**. Instead, 2-isopropyl-1-alkyl-1*H*-imidazol-5(4*H*)-ones **4** were formed in 40–69% yield over three steps (Scheme 1).<sup>†</sup> Notably, for re-

producible results, acylation of **1** should be performed in the absence of any HCl scavenger as described in the literature,<sup>16</sup> with removal of gaseous HCl from crude **2** by co-evaporation with  $\text{CH}_2\text{Cl}_2$ .

1*H*-Imidazol-5(4*H*)-ones **4** are of high medicinal and biological relevance as they are principal structural component of fluorescent protein fluorophores,<sup>17,18</sup> which are gaining prominence as fluorescent biosensor probes.<sup>19,20</sup> Their synthesis usually entails multistep sequences involving, as a key step, azo-Wittig reaction of azidoacetic acid imides,<sup>21</sup> cyclocondensation



**Scheme 1** Reagents and conditions: i,  $\text{RNH}_2$ ,  $\text{MgSO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , room temperature, 18 h; ii,  $\text{ClCH}_2\text{COCl}$ ,  $\text{CH}_2\text{Cl}_2$ , room temperature, 18 h; iii,  $\text{NaN}_3/\text{Al}_2\text{O}_3$ , THF, 110 °C, MW, 1 h.

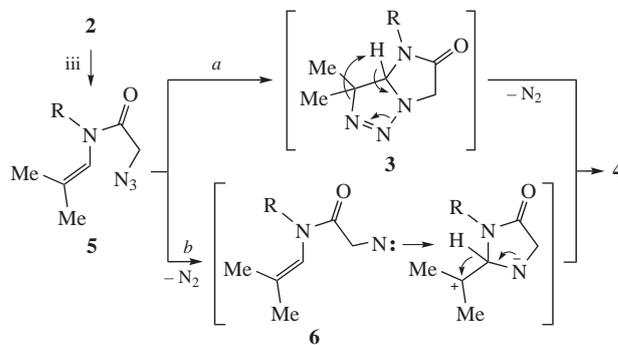
**1*H*-Imidazol-5(4*H*)-ones **4** (general procedure).** Isobutyric aldehyde (20 mmol) and an aliphatic amine (10 mmol) were combined in  $\text{CH}_2\text{Cl}_2$  (10 ml). Anhydrous  $\text{MgSO}_4$  (1.5 g) was added and the mixture was stirred at room temperature for 18 h. The solids were filtered off and the filtrate was concentrated *in vacuo*. The resulting Schiff base **1** (2.5 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 ml) and treated, dropwise, with a solution of chloroacetyl chloride (2.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml). The mixture was stirred at room temperature for 18 h and concentrated *in vacuo*. The gaseous HCl formed in the course of acylation of **1** was additionally co-evaporated with  $\text{CH}_2\text{Cl}_2$  (3×5 ml). The resulting slightly coloured oil (0.5 mmol) containing 70–85% of **2** according to  $^1\text{H}$  NMR analysis, was dissolved in THF (5 ml) and the solution was added to a 5 ml microwave reactor vial containing  $\text{NaN}_3$  (1.5 mmol) absorbed on column chromatography grade  $\text{Al}_2\text{O}_3$  (1:5 w/w). The vigorously stirred mixture was irradiated at 110 °C (50 W, 2 bar) in a microwave reactor for 1 h. The solids were filtered off, washed with copious amount of THF, concentrated *in vacuo* and the desired product was isolated by column chromatography on silica gel using 0 → 10%  $\text{Pr}^i\text{OH}$  in  $\text{CH}_2\text{Cl}_2$  as the eluent.

<sup>†</sup> NMR spectra were recorded in  $\text{CDCl}_3$  using a Bruker Avance III spectrometer (400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$ , relative to TMS). Mass spectra were recorded on a Bruker microTOF spectrometer (electrospray ionization, positive ions detection). Column chromatography was carried out on silica gel 60 (0.040–0.063 mm). MW experiments were implemented by a Biotage Initiator+ microwave reactor. Monitoring of processes was realized using TLC.

of amino acid amides and carboxylic acid components (as ortho esters<sup>22</sup> or imino esters<sup>23</sup>), intramolecular cyclization of amidine-substituted acetic acid derivatives<sup>24</sup> or biomimetic cyclodehydration of dipeptide fragments.<sup>25</sup> To the best of our knowledge, compound **4** has never been reported as prepared in an atom economical and practically convenient fashion as described herein.

The formation of **4** in the reaction of **2** with NaN<sub>3</sub> under microwave irradiation can be rationalized by two alternative plausible mechanisms. The reaction obviously proceeded *via* displacement of the chloride with azide anion to give  $\alpha$ -azidoacetamide **5**. The latter could really undergo the Huisgen-type 1,3-dipolar cycloaddition (intended for it initially) to form **3** which, due to somewhat strained nature, could lose a nitrogen molecule<sup>26</sup> *via* a concerted process and afford **4**. However, said cycloaddition may not be a feasible evolution path for **5** and it may lose a nitrogen molecule first, to give nitrene **6**, in which the reactive nitrogen center can be intercepted intramolecularly and provide observed products **4** (Scheme 2). In order to select between these two mechanistic interpretations, additional studies will be required.

In summary, we have reported a practical procedure to access biologically important 1*H*-imidazol-5(4*H*)-ones *via* an unexpected



Scheme 2

course of the reaction between *N*-chloroacetyl enamines and sodium azide under microwave irradiation.

This work was supported by the Russian Science Foundation (grant no. 14-50-00069). NMR spectroscopy and mass spectrometry studies were performed at the Research Centre for Magnetic Resonance, the Centre for Chemical Analysis and Materials Research of Research park of St. Petersburg State University.

#### Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.01.031.

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- 1-Butyl-2-isopropyl-1H-imidazol-5(4H)-one 2a.* Yield 40%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.95 (t, 3H, Me, *J* 7.4 Hz), 1.28 (d, 6H, Me, *J* 6.7 Hz), 1.30–1.40 (m, 2H, CH<sub>2</sub>), 1.53–1.61 (m, 2H, CH<sub>2</sub>), 2.71 (br. sept, 1H, CH, *J* 6.9 Hz), 3.47 (t, 2H, CH<sub>2</sub>N, *J* 7.6 Hz), 4.05 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 1.2 Hz]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 13.6, 20.1 (3C), 27.7, 31.4, 40.2, 58.2, 170.7, 182.0. HRMS, *m/z*: 183.1485 [M + H]<sup>+</sup> (calc. for C<sub>10</sub>H<sub>19</sub>N<sub>2</sub>O, *m/z*: 183.1492).
- 1-Benzyl-2-isopropyl-1H-imidazol-5(4H)-one 2b.* Yield 69%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.17 (d, 6H, Me, *J* 6.8 Hz), 2.62 (br. sept, 1H, CH, *J* 6.8 Hz), 4.20 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 0.9 Hz], 4.75 [s, 2H, CH<sub>2</sub>(Ar)], 7.20 [d, 2H, 2,2'-CH(Ar), *J* 7.0 Hz], 7.28–7.37 [m, 3H, CH(Ar)]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.9, 28.0, 43.6, 58.2, 126.8, 127.9, 129.0, 136.2, 170.8, 181.8. HRMS, *m/z*: 217.1334 [M + H]<sup>+</sup> (calc. for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O, *m/z*: 217.1335).
- 1-(4-Methylbenzyl)-2-isopropyl-1H-imidazol-5(4H)-one 2c.* Yield 46%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.16 (d, 6H, Me, *J* 6.8 Hz), 2.33 [s, 3H, Me(Ar)], 2.62 (br. sept, 1H, CH, *J* 6.8 Hz), 4.16 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 1.2 Hz], 4.69 [s, 2H, CH<sub>2</sub>(Ar)], 7.08 [d, 2H, 2,2'-CH(Ar), *J* 8.1 Hz], 7.14 [d, 2H, 3,3'-CH(Ar), *J* 7.9 Hz]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.9, 21.1, 28.0, 43.3, 58.2, 126.8, 129.6, 133.2, 137.6, 170.8, 181.8. HRMS, *m/z*: 231.1490 [M + H]<sup>+</sup> (calc. for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O, *m/z*: 231.1492).
- 1-(4-Methoxybenzyl)-2-isopropyl-1H-imidazol-5(4H)-one 2d.* Yield 50%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.16 (d, 6H, Me, *J* 6.7 Hz), 2.63 (br. sept, 1H, CH, *J* 6.9 Hz), 3.78 [s, 3H, MeO(Ar)], 4.15 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 1.0 Hz], 4.66 [s, 2H, CH<sub>2</sub>(Ar)], 6.85 [d, 2H, 2,2'-CH(Ar), *J* 8.7 Hz], 7.12 [d, 2H, 3,3'-CH(Ar), *J* 8.7 Hz]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.9, 28.0, 43.1, 55.3, 58.1, 114.3, 128.2, 128.3, 159.2, 170.8, 181.8. HRMS, *m/z*: 247.1430 [M + H]<sup>+</sup> (calc. for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>, *m/z*: 247.1441).
- 1-(4-Fluorobenzyl)-2-isopropyl-1H-imidazol-5(4H)-one 2e.* Yield 56%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.16 (d, 6H, Me, *J* 6.7 Hz), 2.60 (br. sept, 1H, CH, *J* 6.7 Hz), 4.16 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 1.2 Hz], 4.69 [s, 2H, CH<sub>2</sub>(Ar)], 6.98–7.06 (m, 2H, 3,3'-CH), 7.14–7.21 (m, 2H, 2,2'-CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.9, 28.0, 42.9, 58.1, 115.9 (d, <sup>2</sup>*J*<sub>CF</sub> 22.0 Hz), 128.6 (d, <sup>3</sup>*J*<sub>CF</sub> 8.0 Hz), 132.1 (d, <sup>4</sup>*J*<sub>CF</sub> 3.0 Hz), 162.3 (d, <sup>1</sup>*J*<sub>CF</sub> 246.5 Hz), 170.4, 181.8. HRMS, *m/z*: 235.1251 [M + H]<sup>+</sup> (calc. for C<sub>13</sub>H<sub>16</sub>FN<sub>2</sub>O, *m/z*: 235.1241).
- 1-(4-Chlorobenzyl)-2-isopropyl-1H-imidazol-5(4H)-one 2f.* Yield 40%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.16 (d, 6H, Me, *J* 6.8 Hz), 2.58 (br. sept, 1H, CH, *J* 6.8 Hz), 4.17 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 1.3 Hz], 4.69 [s, 2H, CH<sub>2</sub>(Ar)], 7.13 [d, 2H, 2,2'-CH(Ar), *J* 8.5 Hz], 7.31 [d, 2H, 3,3'-CH(Ar), *J* 8.6 Hz]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.9, 28.0, 43.0, 58.1, 128.2, 129.1, 133.8, 134.8, 170.3, 181.7. HRMS, *m/z*: 251.0953 [M + H]<sup>+</sup> (calc. for C<sub>13</sub>H<sub>16</sub>ClN<sub>2</sub>O, *m/z*: 251.0946).
- 1-(4-Chlorophenethyl)-2-isopropyl-1H-imidazol-5(4H)-one 2g.* Yield 45%, yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.16 (d, 6H, Me, *J* 6.9 Hz), 2.34 (br. sept, 1H, CH, *J* 6.9 Hz), 2.88 (t, 2H, CH<sub>2</sub>N, *J* 7.4 Hz), 3.68 (t, 2H, CH<sub>2</sub>, *J* 7.3 Hz), 4.05 [d, 2H, CH<sub>2</sub>(CO), <sup>4</sup>*J* 0.6 Hz], 7.09 [d, 2H, 2,2'-CH(Ar), *J* 7.8 Hz], 7.28 [d, 2H, 3,3'-CH(Ar), *J* 8.3 Hz]. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 19.7, 27.6, 34.3, 41.9, 58.1, 128.9, 130.2, 132.8, 136.2, 170.3, 181.9. HRMS, *m/z*: 265.1112 [M + H]<sup>+</sup> (calc. for C<sub>14</sub>H<sub>18</sub>ClN<sub>2</sub>O, *m/z*: 265.1102).

Received: 8th August 2016; Com. 16/5021