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Schwartz reagent mediated synthesis of thiazolones and imidazolones from thiazolidine-2,4-diones and imidazolidine-2,4-diones

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ABSTRACT

A novel reduction/elimination method of thiazolidine-2,4-dione and imidazolidine-2,4-dione derivatives using Schwartz reagent to synthesize numerous thiazolones and imidazolones in a single step is reported.

Imidazolone motifs are prevalent in many natural products[1] and have been used in the development of novel drug molecules.[2] Thiazolone-based compounds are known to act as anticancer agents,[3] generally, imidazolones and thiazolones are prepared from their imidazolidine-2,4-dione and thiazolidine-2,4-dione precursors by the metal hydride reduction of the lactam carbonyl group and the subsequent dehydration of lactamol.[4] Recently, during the course of this study, a catalytic monoreduction of imidazolidine-2,4-diones using tetra-*n*-butylammonium fluoride and polymethylhydrosilaxane to obtain imidazolones has been reported.[5] We have previously prepared the N-alkylated imidazolone precursors in two steps, by $LiAlH_4$ or $NaBH_4$ reduction of hydantoin derivatives followed by an elimination using MsCl and excess of DIPEA.[6]

Schwartz reagent ($Cp_2Zr(H)Cl$) mediated hydrozirconation of alkenes and alkynes has been widely used in organic synthesis.[7] Owing to its outstanding usefulness as a hydrozirconation reagent and the ease of preparation, the scope and limitations of $Cp_2Zr(H)Cl$ have been well investigated.[8] The hydridic character of $Cp_2Zr(H)Cl$ has also been demonstrated in its ability to reduce a variety of carbonyl functionalities to Zr alkoxides at a rate competitive with alkene and alkyne hydrozirconation.[8g] It reduces nitrlies,[8e,g] isonitriles, epoxides, esters, ketones,[9a] thioketones,[9b] aldehydes,[9c] lactones,[9d] lithium enolates,[9e] silyl esters,[9f,g] benzyl esters, *t*-butyl esters,[9h] phosophine oxides and sulfides.[9i] Ganem and co-workers have developed a method to prepare the imine intermediates by a selective reduction of secondary amides and lactams using $Cp_2Zr(H)Cl$ in THF followed by a nonaqueous work-up.[10] The chemoselective reduction of tertiary amides to aldehydes via $Cp_2Zr(H)Cl$ was studied in detail by Georg and co-workers.[11] Herein, we report our findings of $Cp_2Zr(H)Cl$ mediated synthesis of thiazolones and imidazolones from their thiazolidine-2,4-dione and imidazolidine-2,4-dione substrates.

During a model study towards the synthesis of α-conhydrine, we attempted to convert 3-(4-bromobut-3-ynyl)thiazolodine-2-4-dione (**1**)[12] into (*Z*)-3-(4-bromobut-3-enyl)thiazolodine-2-4-dione (**3**) using dicyclohexylborane.[13] This reaction resulted in an inseparable (1:2) mixture of **3** and starting material **1**. We next focused our attention on using Schwartz reagent. In the literature, there are many reports on the hydrozirconation of alkyl or aromatic disubstituted alkynes[8] but, to the best of our knowledge, there are none on alkynes substituted with a halogen group. When **1** was reacted with $Cp_2Zr(H)Cl$ (2 equiv), in anhydrous THF at ambient temperature, we were surprised to see that a reduction/elimination reaction occurred giving 3-(4-bromobut-3-ynyl)thiazol-2(3*H*)-one (**2**) as the only product with some unreacted starting material **1** (Scheme 1). Attempts to consume **1** by using excess of $Cp_2Zr(H)Cl$ (3–4 equiv) were not successful and resulted in a mixture of products **2** and **1** in a ratio of 8:1 (based on ^1H NMR spectrum). Due to the apparent diminished reactivity of the bromo alkyne, this observation demonstrates the ability of **1** to undergo a selective lactam reduction/elimination reaction over the hydrozirconation.

Moreover, we were also interested in exploring the preference of reduction/elimination reaction over the hydrozirconation on a

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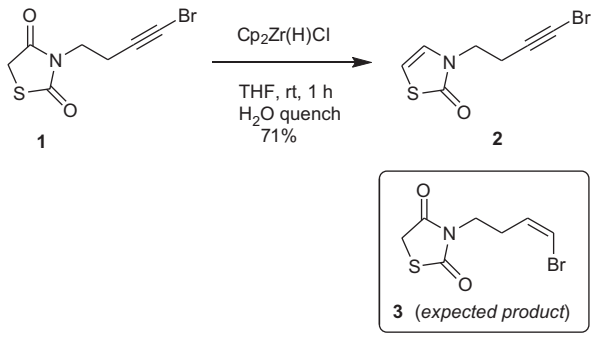


Scheme 1.

suitable substrate. Accordingly, we treated 3-(but-3-ynyl)thiazolidine-2,4-dione (**4**) with varying amounts of $Cp_2Zr(H)Cl$ at different temperatures and the results are summarized in Table 1. All the reactions resulted in the inseparable mixtures of product **5** (both reduction/elimination and hydrozirconation), byproducts **6** (hydrozirconation) and **7** (reduction/elimination), and the recovered **4** in varying amounts (Table 1, entries 1–5). Upon raising the amount of $Cp_2Zr(H)Cl$ to 4 equiv and carrying the reaction at room temperature gave **5** predominantly in 65% yield (Table 1, entry 5).

Encouraged by these results, we envisioned exploring the potential of this reaction on a variety of thiazolidine-2,4-dione, imidazolidine-2,4-dione and oxazolidine-2,4-dione derivatives using commercially available $Cp_2Zr(H)Cl$.[14] Firstly, thiazolidine-2,4-dione (**8a**) was treated with $Cp_2Zr(H)Cl$ to obtain the reduction/elimination product, thiazol-2(3*H*)-one (**11a**) in 76% yield without the formation of any imine product (Table 2, entry 1). Similarly, imidazolidine-2,4-dione (**9a**) was reacted with $Cp_2Zr(H)Cl$ to give 1*H*-imidazol-2(3*H*)-one (**12a**) in good yield (Table 2, entry 4).

All the *N*-alkyl thiazolidine-2,4-diones, *N*-alkyl imidazolidine-2,4-diones and *N,N′*-dialkyl imidazolidine-2,4-diones needed for this study were prepared by following our previously reported method.[6] Interestingly, the *N*-alkyl thiazolidine-2,4-diones **8b**[15] and **8c**,[16] *N*-alkyl imidazolidine-2,4-diones **9b**, **9c** and **9d** and *N,N′*-dialkyl imidazolidine-2,4-diones **9e**,[17] **9f** and **9g** on treatment with $Cp_2Zr(H)Cl$ underwent the clean reduction/elimination reactions to provide the corresponding thiazolone and imidazolone derivatives in good to excellent yields (Table 2, entries 2–3 and 5–10).

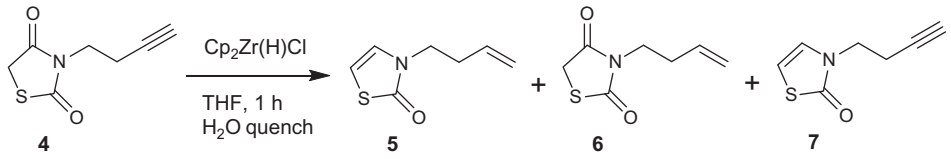
After having success with *N*-alkyl thiazolidine-2,4-dione and imidazolidine-2,4-dione substrates, we next attempted the reduction/elimination of 3-(4-bromobut-3-ynyl)oxazolidine-2,4-dione (**10**) using $Cp_2Zr(H)Cl$ under the standard reaction conditions. The careful monitoring of reaction showed a complete disappearance of **10** by TLC after 10 min, but it reappeared after quenching (Table 2, entry 11) indicating a strong coordination complex formation without any hydride insertion. No expected product was observed even after using excess reagent and extended reaction times.

After the successful reduction/elimination of lactam functionality of *N*-mono/dialkyl imidazolidine-2,4-diones, we were interested in examining a substrate with a *N*-alkoxycarbonyl lactam moiety. Accordingly, *tert*-butyl 3-(2-iodobenzyl)-2,4-dioxoimidazolidine-1-carboxylate (**14**) was treated with $Cp_2Zr(H)Cl$. The expected reduction/elimination product was not formed, instead, it gave the lactamol **15** (Table 3, entry 1). This observation has some close resemblance to the very recent report by Piperno et al. in which the lactamols were formed from *N*-alkoxycarbonyl lactams.[18] We then, investigated the reaction of $Cp_2Zr(H)Cl$ on 1,3-dibenzyldihydropyrimidine-2,4(1*H*,3*H*)-dione (**16**).[19] Again, only the lactamol product **17** was obtained (Table 3, entry 2). Finally, 1-benzylpiperidin-2-one (**18**)[20] and 1-(2-bromophenethyl)pyrrolidine-2,5-dione (**19**)[21] were treated with Schwartz reagent. They only formed the coordination complexes with the reagent and reappeared after quenching (Table 3, entries 3 and 4).

Mechanistically, the $Cp_2Zr(H)Cl$ mediated reduction/elimination reaction is assumed to proceed by a simple hydride addition to the lactam carbonyl group of thiazolidine-2,4-dione, imidazolidine-2,4-dione and their *N*-alkylated derivatives thereby forming a highly moisture sensitive Zr alkoxide complex **II**.[22] In the presence of water, the lone pair electrons of nitrogen induces the elimination of $Cp_2ZrCl(O)^-$ forming an unstable iminium cation derivative **IV**,[23] which can instantaneously rearrange to the most stable cyclic enamine product **V** (Fig. 1). During the course of our studies, Oda et al. have recently shown the successful trapping of the iminium ion in the acid mediated direct allylation of tertiary amides.[24] A mechanistic study of our Schwartz reagent mediated reduction/elimination of *N*-alkyl thiazolidine-2,4-diones and *N*-alkyl imidazolidine-2,4-diones is under investigation and the results will be reported in due course. Since the electron donating ability of lactam nitrogen is compromised for *N*-alkoxycarbonyl imidazolidine-2,4-diones, they only give alcohols upon quenching.

In conclusion, we have reported a novel reduction/elimination method of thiazolidine-2,4-dione and imidazolidine-2,4-dione derivatives using Schwartz reagent to synthesize numerous thiazolones and imidazolones in good to excellent yields in a single step.[25,26] This methodology avoids the traditional two step sequence to prepare the target compounds.

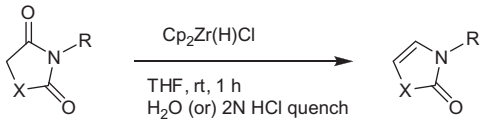
Table 1
Schwartz reagent mediated hydrozirconation and reduction/elimination reactions



Entry	Reagent (Equiv)	Conditions	Product **5**[a] (%)	Byproducts		SM
				6[a] (%)	**7**[a] (%)	**4**[a] (%)
1	2	−10 °C	<1	10	7	81
2	2	0 °C	11	27	11	51
3	2	rt	72	8	2	18
4	3	rt	87	9	2	2
5	4	rt	>97 (65[b])	<1	<1	<1

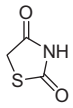
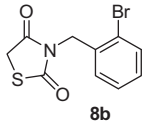
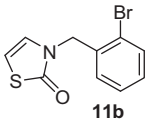
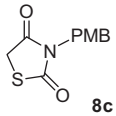
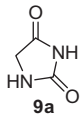
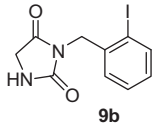
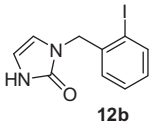
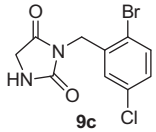
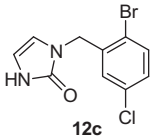
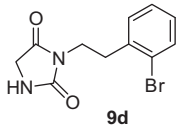
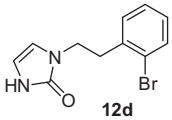
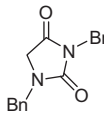
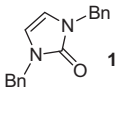
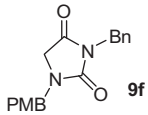
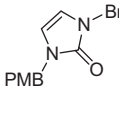
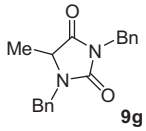
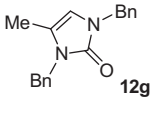
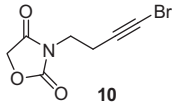
[a] The comparative yields are determined by ^1H NMR analysis of crude mixtures.
[b] Isolated yield.

Table 2
Schwartz reagent mediated reduction/elimination



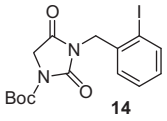
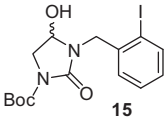
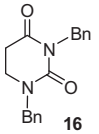
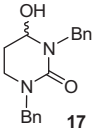
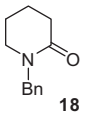
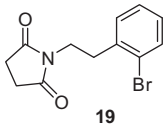
8 : X = S
9 : X = NH, NR
10 : X = O

11 : X = S
12 : X = NH, NR
13 : X = O

Entry	Substrate[a]	Product	Yield[b] (%)
1	 **8a**	 **11a**	76
2	 **8b**	 **11b**	69
3	 **8c**	 **11c**	78
4	 **9a**	 **12a**	71
5	 **9b**	 **12b**	76
6	 **9c**	 **12c**	84
7	 **9d**	 **12d**	85
8	 **9e**	 **12e**	96
9	 **9f**	 **12f**	95
10	 **9g**	 **12g**	72
11	 **10**	–	SM[c]

[a] Conditions: 2 equiv of Schwartz reagent used.
[b] Isolated yields, all the products were identified either with authentic commercially available samples or the reported data, or new, fully characterized by ^{1}H NMR, ^{13}C NMR and MS.
[c] Starting material recovered.

Table 3
Schwartz reagent mediated reduction reactions

Entry	Substrate[a]	Product	Yield[b] (%)
1	 **14**	 **15**	86
2	 **16**	 **17**	80
3	 **18**	–	SM[c]
4	 **19**	–	SM[c]

[a] Conditions: Schwartz reagent (2 equiv).
[b] Isolated yields.
[c] Starting material recovered.

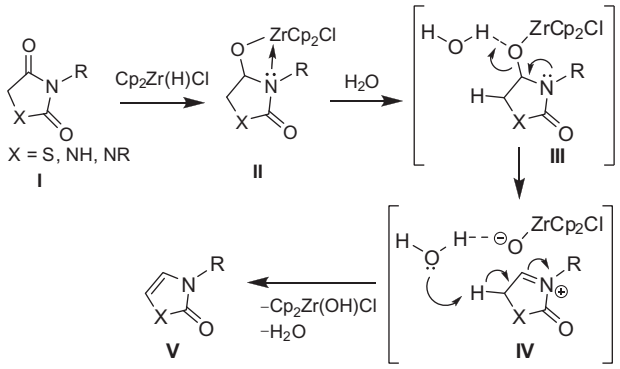


Figure 1. Plausible reaction mechanism.

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Supplementary data

Supplementary data (^{1}H & ^{13}C NMR spectra of all new final products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.015.

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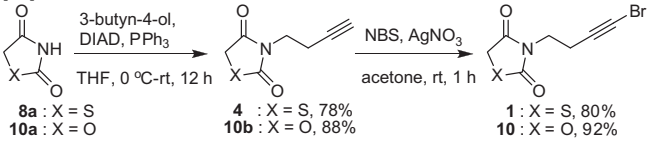
12. (4-Bromobut-3-ynyl)thiazolidine-2,4-dione (**1**) was prepared from **8a** by the Mitsunobu reaction of 3-butyn-4-ol and subsequent bromination by NBS and $AgNO_3$. Similarly, 3-(4-bromobut-3-ynyl)oxazolidine-2,4-dione (**10**) is prepared from **10a**



8a : X = S
10a : X = O
4 : X = S, 78%
10b : X = O, 88%
1 : X = S, 80%
10 : X = O, 92%

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14. After several experiment trials, the optimal reaction conditions were identified, that is 2 equiv $Cp_2Zr(H)Cl$, THF as a solvent, and the reaction duration as 1 h at ambient temperature. Although the suspension in reaction mixture got cleared after 10–15 min indicating the complete disappearance of starting material by TLC, the early quenching with water (or) 2 N HCl resulted in the reappearance of the starting compound. This could be due to the strong complexation of oxygen atoms of the substrate with the highly oxophilic Zr atom of the reagent.
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21. 1-(2-Bromophenethyl)pyrrolidine-2,5-dione (**19**) was prepared from succinic anhydride and 2-bromophenethyl amine in 90% yield according to the procedure reported in Verschueren, W. G.; Dierynck, I.; Amssoms, K. I. E.; Hu, L.; Boonants, P. M. J. Z.; Pille, G. M. E.; Daeyaert, F. F. D.; Hertogs, K.; Surleraux, D. L. N. G.; Wigerinck, P. B. T. P. *J. Med. Chem.* **2005**, *48*, 1930–1940.
22. The Zr alkoxide complex **II** is quite stable under anhydrous conditions. See the Supplementary data for the copies of ^1H & ^{13}C NMR spectra.
23. For a recent mechanistic study, see: Wang, J.; Xu, H.; Gao, H.; Su, C.-Y.; Chao, C.; Phillips, D. L. *Organometallics* **2010**, *29*, 42–51.
24. For a recent report on iminium ion trapping under acidic conditions, see: Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950–953.
25. *General experimental procedure for Schwartz reagent mediated reduction/elimination*: To a suspension of $Cp_2Zr(H)Cl$ (0.63 mmol) in anhydrous THF (2 mL) was added a substrate (0.31 mmol) in THF (1 mL) at room temperature and stirred under nitrogen for 1 h. Water (2 mL) was added to the mixture and kept stirring for 10 min. Then, it was extracted with EtOAc (20 mL), washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude compound was purified by flash silica gel column chromatography to afford a pure product. *Note*: The reactions involving **9a**–**9d** are treated with 2 N HCl for 10 min to affect the complete cleavage of the complex materials, and then neutralized with aqueous sat. $NaHCO_3$ solution.
26. Spectroscopic data of the selected final products:
3-(4-Bromobut-3-ynyl)thiazol-2(3H)-one (***2***): Light orange syrup. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.61 (t, 2H, J = 6.5 Hz), 3.85 (t, 2H, J = 6.5 Hz), 6.12 (d, 1H, J = 5.5 Hz), 6.64 (d, 1H, J = 5.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 20.3, 41.2, 43.9, 76.3, 101.1, 124.7, 171.8. APCI/ESI-MS: m/z 232 $[M+H]^+$. *3-(But-3-enyl)thiazol-2(3H)-one* (***11b***): Colorless syrup. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.44 (q, 2H, J = 7.0 Hz), 3.77 (t, 2H, J = 7.0 Hz), 5.07–5.13 (m, 2H), 5.72–5.81 (m, 1H), 6.09 (d, 1H, J = 5.5 Hz), 6.53 (d, 1H, J = 5.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 33.4, 44.7, 100.9, 118.0, 124.5, 133.8, 171.9. APCI/ESI-MS: m/z 156 $[M+H]^+$. *3-(2-Bromobenzyl)thiazol-2(3H)-one* (***11c***): White solid, mp: 90–92 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.99 (s, 2H), 6.13 (d, 1H, J = 5.5 Hz), 6.58 (d, 1H, J = 5.5 Hz), 7.19 (dt, 1H, J = 1.5, 8.0 Hz), 7.23 (dd, 1H, J = 1.5, 8.0 Hz), 7.31 (dt, 1H, J = 1.0, 8.0 Hz), 7.58 (dd, 1H, J = 1.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 48.5, 101.5, 123.2, 124.2, 128.0, 129.7, 129.8, 133.0, 135.0, 172.0. APCI/ESI-MS: m/z 270 $[M+H]^+$. *3-(4-Methoxybenzyl)thiazol-2(3H)-one* (***11d***): Off-white solid, mp: 84–86 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.80 (s, 3H), 4.80 (s, 2H), 6.07 (d, 1H, J = 5.5 Hz), 6.46 (d, 1H, J = 5.5 Hz), 6.88 (d, 2H, J = 8.5 Hz), 7.21 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 48.1, 55.3, 101.3, 114.3, 124.0, 128.0, 129.4, 159.5, 171.9. APCI/ESI-MS: m/z 222 $[M+H]^+$. *1-(2-Iodobenzyl)-1H-imidazol-2(3H)-one* (***12b***): White solid, mp: 105–107 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.85 (s, 2H), 6.17 (s, 1H), 6.34 (s, 1H), 6.99 (t, 1H, J = 7.5 Hz), 7.09 (d, 1H, J = 7.5 Hz), 7.32 (t, 1H, J = 8.0 Hz), 7.85 (d, 1H, J = 8.0 Hz), 10.97 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 51.4, 98.0, 108.9, 111.3, 128.5, 128.7, 129.4, 138.9, 139.5. APCI/ESI-MS: m/z 301 $[M+H]^+$. *1-(2-Bromo-5-chlorobenzyl)-1H-imidazol-2(3H)-one* (***12c***): White solid, mp: 158–160 °C. ^1H NMR (500 MHz, $CDCl_3$+CD_3OD) δ (ppm) 4.87 (s, 2H), 6.31 (d, 1H, J = 3.0 Hz), 6.39 (d, 1H, J = 3.0 Hz), 7.09 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5, 8.5 Hz), 7.54 (d, 1H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD) δ (ppm) 46.0, 1.08.4, 111.3, 120.1, 128.4, 128.9, 133.4, 133.6, 137.3, 153.7. APCI/ESI-MS: m/z 287 $[M+H]^+$. *1-(2-Bromophenethyl)-1H-imidazol-2(3H)-one* (***12d***): Colorless syrup. ^1H NMR (500 MHz, CD_3OD) δ (ppm) 3.12 (t, 2H, J = 7.0 Hz), 3.88 (t, 2H, J = 7.0 Hz), 6.20 (d, 1H, J = 3.0 Hz), 6.30 (d, 1H, J = 3.0 Hz), 7.10–7.14 (m, 1H), 7.22–7.27 (m, 2H), 7.55 (d, 1H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 36.0, 42.9, 107.8, 111.8, 124.5, 127.6, 128.4, 131.3, 132.9, 137.5, 154.5. APCI/ESI-MS: m/z 267 $[M+H]^+$. *1-Benzyl-3-(4-methoxybenzyl)-1H-imidazol-2(3H)-one* (***12f***): Light brown syrup. ^1H NMR (500 MHz, CD_3OD) δ (ppm) 3.79 (s, 3H), 4.75 (s, 2H), 4.81 (s, 2H), 6.07 (s, 2H), 6.86 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.24–7.29 (m 3H), 7.31–7.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 46.7, 47.2, 55.2, 110.1 (2), 114.1, 127.7, 127.8, 128.7, 129.0, 129.3, 137.0, 159.2. APCI/ESI-MS: m/z 295 $[M+H]^+$. *1,3-Dibenzyl-4-methyl-1H-imidazol-2(3H)-one* (***12g***): Light orange syrup. ^1H NMR (500 MHz, CD_3OD) δ (ppm) 1.86 (d, 3H, J = 1.5 Hz), 4.79 (s, 2H), 4.86 (s, 2H), 5.84 (d, 1H, J = 1.5 Hz), 7.22–7.34 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 10.4, 44.5, 46.9, 106.2, 119.0, 126.9, 127.3, 127.6, 127.8, 128.6 (3), 137.2, 137.6, 153.7. APCI/ESI-MS: m/z 279 $[M+H]^+$. *Tert-butyl 4-hydroxy-3-(2-iodobenzyl)-2-oxoimidazolidine-1-carboxylate* (***15***): White solid, mp: 150–152 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.52 (s, 9H), 3.71 (dd, 1H, J = 1.5, 12.0 Hz), 3.84 (dd, 1H, J = 7.0, 12.0 Hz), 4.42 (d, 1H, J = 16.0 Hz), 4.49 (d, 1H, J = 7.5 Hz, OH), 4.73 (d, 1H, J = 16.0 Hz), 5.01 (t, 1H, J = 7.5 Hz), 6.96 (dt, 1H, J = 1.5, 8.0 Hz), 7.30 (dt, 1H, J = 1.0, 7.5 Hz), 7.35 (dd, 1H, J = 1.5, 8.0 Hz), 7.81 (dd, 1H, J = 1.5, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 28.1, 48.7, 50.4, 75.4, 83.0, 98.8, 128.5, 129.3, 129.8, 138.7, 139.6, 150.4, 153.4. APCI/ESI-MS: m/z 363 $[(M-t\text{-Bu})+2H]^+$. *1,3-Dibenzyl-4-hydroxytetrahydropyrimidin-2(1H)-one* (***17***): Colorless syrup. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.79–1.86 (m, 2H), 3.00–3.05 (m, 1H), 3.49–3.59 (m, 2H), 4.43 (d, 2H, J = 15.5 Hz), 4.73 (d, 1H, J = 15.0 Hz), 4.87 (s, 1H), 4.91 (d, 1H, J = 15.0 Hz), 7.22–7.33 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 28.9, 40.0, 49.3, 51.5, 77.7, 127.2, 127.3, 127.7, 127.8, 128.5, 128.7, 138.0, 139.0, 155.2. APCI/ESI-MS: m/z 297 $[M+H]^+$.