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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 4912–4917

N-Arylimidazole synthesis by cross-cycloaddition of isocyanides using a novel catalytic system

Marc-André Bonin, Denis Giguère and René Roy*

Department of Chemistry, Université du Québec à Montréal, PO Box 8888, Suc. Centre-Ville, Montréal, QC H3C 3P8, Canada

Received 19 January 2007; revised 22 March 2007; accepted 23 March 2007
Available online 30 March 2007

Abstract—A direct catalytic synthesis of *N*-arylimidazoles starting from the corresponding *N*-arylformamides and *N*-formylglycine esters is described. Application to different aryl substituted electron-withdrawing and -donating groups provided the analogous heterocyclic compounds in very high yields. The use of copper(I) oxide/proline catalysts allowed the reactions to proceed at room temperature. The first synthesis of *N*-arylimidazole bearing carbohydrate moieties is also described.

1. Introduction

Imidazole derivatives are found in several natural products.[1] They display widespread applications in organic synthesis and constitute important pharmacophores.[2] As such, wide interests have been devoted at developing new and efficient methodologies toward the synthesis of *N*-aryl-containing imidazoles. Losartan[3] (antihypertension), Etomidate[4] (hypnotic agent), and Flumazenil[5] (benzodiazepine antagonist) are a few examples of arylimidazole-containing drugs widely used. Due to their extensive and useful relevance and properties, several methodologies have been developed for the synthesis of the core imidazole ring.[2,6] This heterocyclic system is usually prepared using Bredereck's synthesis or by cyclization between *p*-tosylmethyl isocyanides and aldimines or imidoyl chlorides. However, only a few catalytic methods exist toward their synthesis.[6a–c] For instance, Abell's group performed the synthesis of trisubstituted imidazoles using palladium-catalyzed cyclization of *O*-pentafluorobenzoyl-amidoximes,[6b] while the heterocoupling between two different isocyanides using copper(I) oxide as catalyst and 1,10-phenanthroline as ligand has been described by Yamamoto and co-workers.[6a] Previously reported procedures required the use of strong base,[6d] high temperature,[6a,b,e] and/or unstable isocyanides as starting materials.[6a,e,g] Thus, a new catalytic methodology that proceed under smooth reaction conditions is required.

The synthesis of imidazoles starting from stable formamides would provide much simpler and efficient strategy toward this goal. Although synthetically useful in organic syntheses, isocyanides can undergo α-addition with both electrophiles and nucleophiles.[7] Unfortunately this functional group is unstable and unpleasant to work with. If crude isocyanides, resulting from dehydration of formamides could be performed straightforwardly, it would constitute a beneficial improvement in isocyanide chemistry. This is, to the best of our knowledge, the first report of a catalytic *N*-arylimidazole synthesis involving crude isocyanides prepared from the corresponding formamides. Herein, a direct catalytic synthesis of *N*-arylimidazoles is described that proceed without the need for purification of unstable isocyanide intermediates. Moreover, a novel catalytic system that allows this reaction to proceed at room temperature is exemplified (Fig. 1). In addition, application of this new methodology toward the first synthesis of carbohydrate-bearing *N*-arylimidazole aglycones is depicted together with a plausible reaction mechanism.

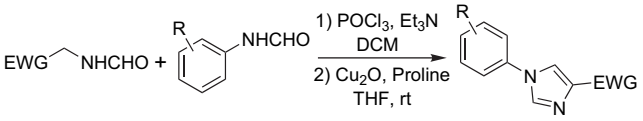

Figure 1. Synthesis of *N*-arylimidazoles by cross-cycloaddition of isocyanides using copper(I) oxide and proline.

2. Results and discussion

The first aim of this study was to synthesize imidazoles starting from *N*-arylformamides[8] and ethyl *N*-formylglycine esters. Several efficient methods are known to convert formyl groups into isocyanides.[9] A general method that could be used for both dehydration of aromatic and aliphatic formamides is however required. After evaluating numerous dehydrating conditions, phosphorus oxychloride/Et_3N appeared to be most appropriate for the above purpose. Only

* Corresponding author. Tel.: +1 514 987 3000x2546; fax: +1 514 987 4054; e-mail: roy.rene@uqam.ca

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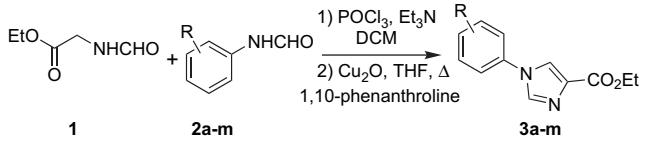
doi:10.1016/j.tet.2007.03.152

Table 1. Catalytic synthesis of *N*-arylimidazoles **3a–m** from *N*-arylformamides **2a–m** and ethyl *N*-formylglycine ester **1** using copper(I) oxide and 1,10-phenanthroline[a]



1 **2a-m** **3a-m**

Entry	Aryl	R	Product (yield,[b] %)
1	**2a**	H	**3a** (95)
2	**2b**	4-OMe	**3b** (92)
3	**2c**	3-OMe	**3c** (96)
4	**2d**	2-OMe	**3d** (65)
5	**2e**	4-NO_2	**3e** (76)
6	**2f**	3-NO_2	**3f** (20)
7	**2g**	2-NO_2	**3g** (10)
8	**2h**	4-Me	**3h** (92)
9	**2i**	3-Me	**3i** (93)
10	**2j**	2-Me	**3j** (95)
11	**2k**	4-Cl	**3k** (91)
12	**2l**	3-Cl	**3l** (92)
13	**2m**	2-Cl	**3m** (97)

[a] Reactions were conducted with 2.96 mmol of **1** and 1.97 mmol of **2a–m** in refluxing THF (<4 h).
[b] Isolated yields.

silica gel filtration of the crude isocyanide mixtures was necessary for their direct use in the cross-cycloadditions, without affecting the overall yields. Table 1 shows the synthesis of *N*-arylimidazoles **3a–m** starting from ethyl *N*-formylglycine ester **1** using a panel of *N*-arylformamides **2a–m**. This direct synthesis of *N*-arylimidazoles tolerated different functionalities at different positions. Thus, *p*-, *m*-, and *o*-methoxyphenyl formamides **2b–d** afforded the corresponding *N*-methoxyarylimidazoles **3b–d** in 92, 96, and 65% yields, respectively (entries 2–4). *N*-(Nitrophenyl)-formamides **2e–g** provided *N*-nitroaryl-imidazoles **3e–g** in lower yields ranging from 76 to 10% (entries 5–7). Finally, methyl- and *N*-(chlorophenyl)-formamides (**2h–m**) gave imidazoles **3h–m** in greater than 91% yields (entries 8–13). Yields given in Table 1 refer to both isocyanide formation and cycloaddition (three operations in total) and only one silica gel chromatography.

Our next attention was directed at using ligands that could allow the reaction to proceed at room temperature. Proline was selected because it is known that amino acids and copper(I) salts can catalyze Ullmann-type reactions and C–N bond formations between aryl halides and amines.[10] To our delight, substitution of 1,10-phenanthroline by proline (Table 2) allowed *N*-arylimidazole synthesis, albeit in slightly lower yields in refluxing THF but in 45 min rather than 3 h (entry 2 compared to 1). Fortuitously, the reaction proceeded even better at room temperature (entry 3). Additionally, lowering the amount of **1** decreased the yield only marginally to 89% (entry 4) and lowering the amount of copper(I) to 1 mol % and proline to 2 mol % (entry 5) did not allow the reaction to proceed satisfactorily.

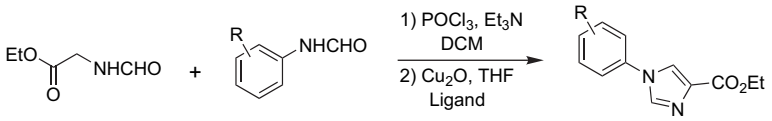
With these optimized ligand and reaction conditions (Table 2, entry 3), the cycloaddition was attempted using **1** and *N*-arylformamides **2b–m**. Interestingly, similar yields were obtained for almost all compounds. Table 3 shows comparative yields between three methods for the synthesis of various *N*-arylimidazoles. The reference method[6a] used preformed isocyanides in refluxing THF, while both methods A (1,10-phenanthroline, refluxing THF) and B (proline, rt) started with crude isocyanides obtained from the corresponding formamides. Both new methods provided similar or better yields than the previous[6a] method for *N*-arylimidazoles **3a**,**d–f**,**h**, and **k**. Proline was even more efficient than 1,10-phenanthroline for the synthesis of *N*-arylimidazoles **3d** and **f**. Synthesis of imidazole **3d**, starting with *N*-(2-methoxyphenyl)formamide **2d**, was accomplished in 76% (Table 3, entry 2) instead of 65% yield (Table 1, entry 4) and synthesis of 4-ethoxycarbonyl-1-(2-nitrophenyl)imidazole **3f** was accomplished in 50% (Table 3, entry 4) instead

Table 3. Comparative yield (%) using various methods for the synthesis of *N*-arylimidazoles **3a**,**d–f**,**h**, and **k**[a]

Entry	*N*-Aryl-imidazoles	Yamamoto[b]	Method A	Method B
1	**3a** (H)	93	95	96
2	**3d** (2-OMe)	88	65	76
3	**3e** (4-NO_2)	88	76	83
4	**3f** (3-NO_2)	—	20	50
5	**3h** (4-Me)	—	92	87
6	**3k** (4-Cl)	93	91	93

[a] See Section 5 for complete experimental details for method A (Cu_2O, 1,10-phenanthroline, rt, and THF) and B (Cu_2O, proline, rt, and THF).
[b] Ref. 6a (Cu_2O, 1,10-phenanthroline, and refluxing THF).

Table 2. Improved procedure for the catalytic synthesis of *N*-arylimidazole using copper(I) oxide and proline[a]



1 **2a, d, f** **3a, d, f**

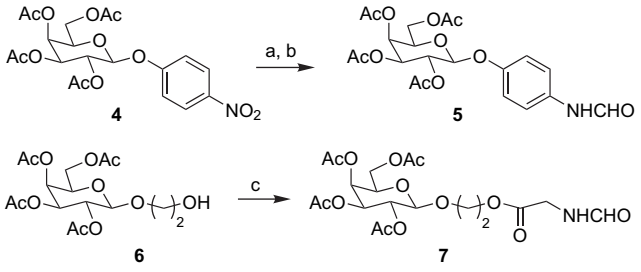
Entry	Ligand	Aryl (R)	Time (h)	Temperature (°C)	Equiv of **1**	Product (yield,[b] %)
1	1,10-Phenanthroline	**2a** (H)	3	79	1.5	**3a** (95)
2	Proline	**2a**	0.75	79	1.5	**3a** (86)
3	Proline	**2a**	1	25	1.5	**3a** (96)
4	Proline	**2a**	1	25	1.0	**3a** (89)
5[c]	Proline	**2a**	3	25	1.5	**3a** (Trace)

[a] Reactions were conducted with 1.5 mmol of **1** and 1.0 mmol of **2a** catalyzed by 10 mol % of Cu_2O and 20 mol % of ligand unless otherwise noted.
[b] Isolated yields.
[c] Reaction was conducted with 1 mol % of Cu_2O and 2 mol % of proline.

of 20% yield (Table 1, entry 6). The yields obtained by method B represent a direct synthesis that proceeded at room temperature and without the need for purification of unstable and noxious isocyanides. Therefore, this method is more appropriate toward heat sensitive compounds. Moreover proline is less expensive than 1,10-phenanthroline and stays in the aqueous layer during work-up.

In continuation of our interest toward the synthesis of heterocyclic glycomimetics for biological applications,[11] this new methodology was used for the synthesis of carbohydrate-containing imidazoles. Syntheses of both *N*-arylformamides and *N*-formylglycine glycosides are described in Scheme 1. Commercially available *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **4** underwent reduction using a catalytic amount of Pd/C (10 mol %) and the newly formed aniline derivative was formylated under acidic conditions to afford *N*-arylformamide **5** in yield comparable to those already published.[12] Furthermore, galactosyl *N*-formylglycyl ester **7** was synthesized in a one-step sequence using a Mitsonubu reaction between 2-hydroxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **6**[13] and commercially available *N*-formylglycine in 87% yield.[14] Both *N*-formyl galactoside **5** and **7** were able to provide imidazole glycomimetics as described in Scheme 2.

Galactoside **5** and ethyl *N*-formylglycine ester **1** were initially dehydrated ($POCl_3$, Et_3N, and DCM) then, the newly formed isocyanides were treated under the copper-catalyzed cross-cycloaddition to provide *N*-arylimidazole **8** in 80% yield. Moreover, galactoside **7** reacted in the same way with *N*-arylformamide **2a** to provide *N*-arylimidazole galactoside **9** in a modest 46% yield. Under this consideration, we envisaged a stepwise strategy and isolated isonitrile **10** in 58% yield, followed by the cycloaddition that produced imidazole **9** in 76% yield.

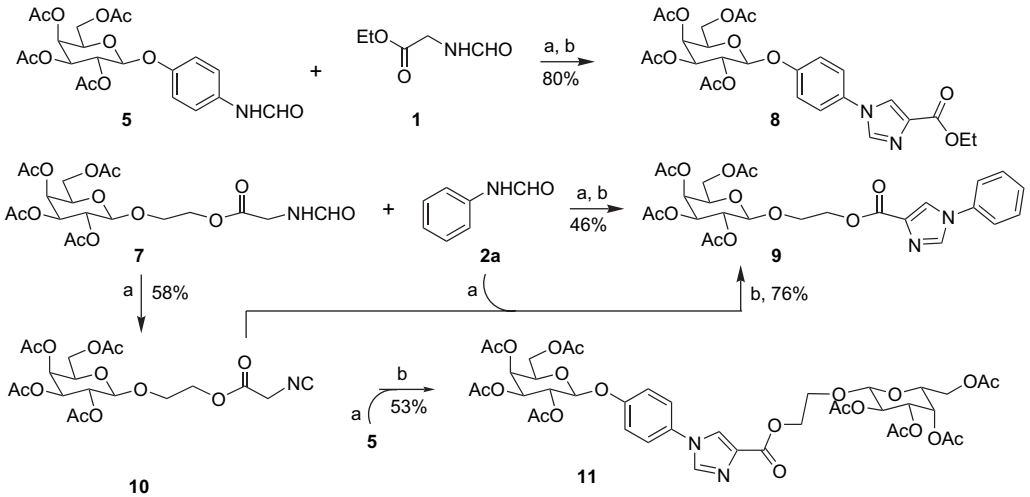


Scheme 1. *Reagent and conditions*: (a) H_2, Pd/C (10 mol %), MeOH; (b) formic acetic anhydride, acetic acid; and (c) DEAD, PPh_3, *N*-formylglycine, THF, 87%.

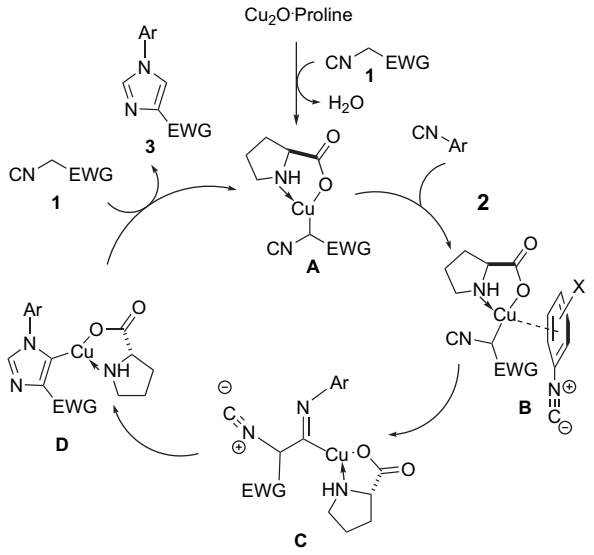
Being also interested by the synthesis of glycoclusters[11a,15] and glycodendrimers,[16] the same strategy toward galactosyl dimer **11** was accomplished next by coupling crude dehydrated galactoside **5** and **10**. The reaction produced *N*-arylimidazole di-galactoside **11** in 53% yield. Interestingly, imidazole is part of the essential amino acid histidine and this simple sequence is efficient to prepare optically active glycopeptide mimetics containing a N-terminal imidazole (glycopeptide **8**). Moreover, this first direct synthesis of imidazole containing carbohydrates did not affect the acid sensitive glycosidic bond or acetate protecting groups.

3. Plausible mechanism

The previously[6a] described mechanism cannot explain why this powerful reaction was effective only with aromatic isocyanides. As depicted in Scheme 3, copper(I) oxide/proline complex could react with ethyl *N*-isocyanide glycine ester **1** through extrusion of water to form intermediate **A**.[17] This chelated copper(I) proline adduct might render the aromatic ring of the π-complex **B** more electron-deficient, thereby facilitating the nucleophilic attack onto the aryl isocyanide at carbon center (**C**). As proline is a weaker chelator than 1,10-phenanthroline to copper(I) oxide, this might explain why using proline as ligand, the reaction occurred at room temperature. π-Complexes mechanism involving copper were initially proposed by Paine[18] for Ullmann-type coupling involving copper(I) and proline.[10a] Intramolecular attack of nitrogen on carbon atom of isocyanide allowed formation of intermediate **D**, which is protonated by **1** to produce *N*-arylimidazole **3**.



Scheme 2. *Reagent and conditions*: (a) $POCl_3$, Et_3N, DCM and (b) Cu_2O, proline, THF, rt.



Scheme 3. Plausible mechanism for copper(I)-catalyzed cross-cycloaddition between isocyanides having a π-complex intermediate **B**.

4. Conclusions

In conclusions, we completed a direct catalytic synthesis of *N*-arylimidazoles through copper(I)-catalyzed cross-cycloaddition between two different isocyanides obtained from their corresponding formamide derivatives. By using proline as ligand it was possible to decrease the reaction temperature without affecting the reaction yields. This new methodology was applied for the first time toward the synthesis of imidazole-bearing glycomimetics and a plausible mechanism was proposed. We believe that using the crude isocyanides in organic synthesis for further transformation is a under exploited strategy. Finally, current progresses are being made toward the synthesis of new imidazole glycomimetics.

5. Experimental

5.1. General methods

All reactions in organic medium were carried out under nitrogen atmosphere using freshly distilled solvents. Evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60-F_{254} precoated plates (E. Merck). Purifications by flash column chromatography were performed using silica gel Si 60 (40–63 μm) with the indicated eluent. NMR spectra were recorded on a Varian Gemini 300 spectrometer. Proton chemical shifts (δ) are reported in parts per million downfield from $CHCl_3$. Coupling constants (J) are reported in hertz (Hz). Melting points (uncorrected) were measured on a Fisher Jones apparatus and optical rotations were measured with a JASCO P-1010 polarimeter. Accurate mass measurements were performed on a LC-MSD-TOF instrument from Agilent Technologies in positive electrospray at the regional MS facility of the University of Montreal by Dr. A. Furtos. Either protonated molecular ions $(M+H)^+$ or sodium adducts $(M+Na)^+$ were used for empirical formula confirmation.

5.1.1. General procedure for *N*-arylimidazole synthesis using copper(I) oxide and 1,10-phenanthroline as catalyst (Method A). To a solution of *N*-arylformamide derivative (1.0 mmol) and glycine formamide derivative (1.5 mmol) in DCM (3.5 mL) were added Et_3N (7.5 mmol) and $POCl_3$ (3.5 mmol) dropwise at 0° C. The reaction was stirred at 0° C until disappearance of the starting materials (usually less than 2 h). After the required amount of time, the mixture was filtered over silica gel (to separate the phosphorus salts from the organic compounds using 4/1 DCM/Et_2O) and concentrated under reduced pressure. The crude residue was dissolved in THF (3.5 mL), Cu_2O (0.1 mmol) and 1,10-phenanthroline (0.2 mmol) were added and stirred under reflux until completion of the reaction (usually less than 4 h). A solution of aq EDTA (5%) (3.5 mL) was added to the reaction mixture, which was then extracted (5×) with ethyl acetate. The crude residue was purified by flash column chromatography using a mixture of ethyl acetate and DCM as an eluent.

5.1.2. General procedure for *N*-arylimidazole synthesis using copper(I) oxide and proline as catalyst (Method B). To a solution of *N*-aryl formamide derivatives (1.0 mmol) and glycine formamide derivative (1.5 mmol) in DCM (3.5 mL) were added Et_3N (7.5 mmol) and $POCl_3$ (3.5 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C until disappearance of the starting materials (usually less than 2 h). After the appropriate time, the mixture was filtered over silica using DCM/Et_2O (4/1) and concentrated under reduced pressure. The crude residue was dissolved in THF (3.5 mL) to which Cu_2O (0.1 mmol) and proline (0.2 mmol) were added and the resulting solution stirred at room temperature until completion of the reaction (usually less than 4 h). A solution of aq EDTA (5%) (3.5 mL) was added to the reaction mixture, which was then extracted (5×) with ethyl acetate. The crude residue was purified by flash column chromatography using a mixture of ethyl acetate and DCM as an eluent.

5.1.2.1. 4-Ethoxycarbonyl-1-(3-nitrophenyl)imidazole (3f). Brown solid, mp 152–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.33–8.29 (m, 2H), 8.04 (d, 1H, J=1.5 Hz), 7.98 (d, 1H, J=1.5 Hz), 7.84–7.74 (m, 2H), 4.41 (q, 2H, J=7.0 Hz), 2.25 (s, 3H), 1.42 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.2, 149.1, 137.3, 136.4, 136.0, 131.3, 127.5, 123.4, 123.0, 116.6, 61.0, 14.3; IR (neat NaCl) cm^{-1}: 3132, 2924, 1697, 1652, 1531, 1101; HRMS *m*/*z* calcd $C_{12}H_{12}N_3O_4$ $[M+H]^+$: 262.0822; found: 262.0826.

5.1.2.2. 4-Ethoxycarbonyl-1-(2-nitrophenyl)imidazole (3g). Orange solid, mp 89–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.11 (dd, 1H, J=8.0, 1.5 Hz), 7.83–7.66 (m, 2H), 7.76 (d, 1H, J=1.5 Hz), 7.66 (d, 1H, J=1.5 Hz), 7.49 (dd, 1H, J=8.0, 1.5 Hz), 4.40 (q, 2H, J=7.0 Hz), 2.25 (s, 3H), 1.40 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.3, 145.0, 138.0, 135.1, 134.2, 130.6, 129.7, 128.9, 126.0, 125.8, 60.9, 14.3; IR (neat NaCl) cm^{-1}: 2924, 1734, 1696, 1652, 1541, 1096; HRMS *m*/*z* calcd $C_{12}H_{12}N_3O_4$ $[M+H]^+$: 262.0822; found: 262.0822.

5.1.2.3. 4-Ethoxycarbonyl-1-(4-methylphenyl)imidazole (3h). White solid, mp 129–131 °C; ^{1}H NMR

(300 MHz, $CDCl_3$, δ ppm): 7.92 (d, 1H, J=1.5 Hz), 7.82 (d, 1H, J=1.5 Hz), 7.34–7.26 (m, 4H), 4.41 (q, 2H, J=7.0 Hz), 2.43 (s, 3H), 1.42 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.7, 146.3, 138.4, 136.2, 134.8, 134.0, 130.5, 124.0, 121.5, 60.6, 20.9, 14.3; IR (neat NaCl) cm^{-1}: 3146, 3117, 2987, 1705, 1555, 1275; HRMS m/z calcd $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128; found: 231.1128.

5.1.2.4. 4-Ethoxycarbonyl-1-(3-methylphenyl)imidazole (3i). White solid, mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.95 (d, 1H, J=1.5 Hz), 7.85 (d, 1H, J=1.5 Hz), 7.40 (t, 1H, J=8.0 Hz), 7.30–7.20 (m, 3H), 4.41 (q, 2H, J=7.0 Hz), 2.44 (s, 3H), 1.42 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.5, 140.2, 136.2, 136.1, 134.7, 129.7, 128.9, 123.8, 122.0, 118.5, 60.5, 21.2, 14.2; IR (neat NaCl) cm^{-1}: 3122, 2977, 1724, 1691, 1546, 1270; HRMS m/z calcd $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128; found: 231.1125.

5.1.2.5. 4-Ethoxycarbonyl-1-(2-methylphenyl)imidazole (3j). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.79 (d, 1H, J=1.5 Hz), 7.66 (d, 1H, J=1.5 Hz), 7.51–7.22 (m, 4H), 4.43 (q, 2H, J=7.0 Hz), 2.25 (s, 3H), 1.45 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.3, 137.8, 135.5, 133.8, 133.1, 131.0, 129.0, 126.7, 125.9, 125.8, 60.1, 17.1, 13.9; IR (neat NaCl) cm^{-1}: 3116, 2978, 1727, 1536, 1498, 1254; HRMS m/z calcd $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128; found: 231.1128.

5.1.2.6. 4-Ethoxycarbonyl-1-(3-chlorophenyl)imidazole (3l). White solid, mp 105–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.95 (d, 1H, J=1.0 Hz), 7.86 (d, 1H, J=1.0 Hz), 7.47–7.26 (m, 4H), 4.41 (q, 2H, J=7.0 Hz), 1.41 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.3, 137.3, 136.0, 135.7, 135.3, 131.1, 128.4, 123.5, 121.8, 119.6, 60.6, 14.2; IR (neat NaCl) cm^{-1}: 3131, 3069, 2991, 1701, 1652, 1541, 1275; HRMS m/z calcd $C_{12}H_{13}ClN_2O_2$ $[M+H]^+$: 251.0582; found: 251.0581.

5.1.2.7. 4-Ethoxycarbonyl-1-(2-chlorophenyl)imidazole (3m). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.83 (d, 1H, J=1.5 Hz), 7.70 (d, 1H, J=1.5 Hz), 7.60–7.57 (m, 1H), 7.47–7.35 (m, 3H), 4.40 (q, 2H, J=7.0 Hz), 2.25 (s, 3H), 1.41 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 162.2, 137.9, 133.9, 133.7, 130.6, 130.1, 129.3, 127.8, 127.2, 125.9, 60.2, 14.0; IR (neat NaCl) cm^{-1}: 3112, 2981, 1729, 1657, 1541; HRMS m/z calcd $C_{12}H_{13}ClN_2O_2$ $[M+H]^+$: 251.0582; found: 251.0580.

5.1.2.8. (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-2-hydroxyethyl *N*-formylglycine ester (7). To a solution of **6** (1.15 mmol, 450 mg), PPh_3 (3.45 mmol, 905 mg), and *N*-formylglycine (4.03 mmol, 415 mg) in THF (5 mL) was added dropwise DEAD (3.45 mmol, 0.68 mL) at 0 °C. The reaction was allowed to warm slowly and stirred for 48 h at room temperature. The mixture was concentrated under reduced pressure and purified by flash chromatography using 100% ethyl acetate affording 478 mg (87%) of pure **7**. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.2 (s, 1H), 6.69 (br t, 1H), 5.32 (dd, 1H, J=3.5, 0.5 Hz), 5.12 (dd, 1H, J=10.5, 8.0 Hz), 4.97 (dd, 1H, J=10.5, 3.5 Hz), 4.48 (d, 1H, J=8.0 Hz), 4.27 (t, 2H, J=5.0 Hz), 4.12–3.87 (m, 7H), 3.77–3.70 (m, 1H), 2.10 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.1, 170.0, 169.4, 169.2, 161.3, 100.9, 70.6, 70.5, 68.4, 66.9, 66.8, 63.9, 61.1, 39.6, 20.6, 20.5 (2C), 20.4; IR (neat NaCl) cm^{-1}: 2919, 2846, 1749, 1734, 1652, 1096; HRMS m/z calcd $C_{19}H_{28}NO_{13}$ $[M+H]^+$: 478.1555; found: 478.1555; $[\alpha]_D^{25}$ −6.9 (c 1.2 in $CHCl_3$).

5.1.2.9. 4-Ethoxycarbonyl-1-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)phenyl]imidazole (8). Compound **8** was isolated as a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.81 (d, 1H, J=1.0 Hz), 7.72 (d, 1H, J=1.0 Hz), 7.26 (d, 2H, J=9.0 Hz), 7.07 (d, 2H, J=9.0 Hz), 5.46–5.39 (m, 2H), 5.09–5.02 (m, 2H), 4.30 (q, 2H, J=7.0, 14.2 Hz), 4.19–4.05 (m, 4H), 2.11 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.32 (t, 3H, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.2, 170.0, 169.9, 169.2, 162.6, 156.5, 136.4, 134.9, 131.7, 127.9, 124.1, 123.2, 118.1, 117.5, 99.3, 71.1, 70.6, 68.4, 66.7, 61.2, 60.6, 20.6, 20.5, 20.4, 14.3; IR (neat, NaCl) cm^{-1}: 3019, 1734, 1653, 1216; HRMS m/z calcd $C_{26}H_{31}N_2O_{12}$ $[M+H]^+$: 563.1872; found: 563.1873; $[\alpha]_D^{25}$ +2.3 (c 0.9 in $CHCl_3$).

5.1.2.10. 4-[2-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosiloxy)ethoxycarbonyl]-1-phenylimidazole (9). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (d, 1H, J=1.0 Hz), 7.82 (d, 1H, J=1.0 Hz), 7.47–7.33 (m, 5H), 5.29 (d, 1H, J=3.0 Hz), 5.14 (dd, 1H, J=10.5, 8.0 Hz), 4.94 (dd, 1H, J=10.5, 3.5 Hz), 4.57 (d, 1H, J=8.0 Hz), 4.46–4.36 (m, 2H), 4.06–4.03 (m, 3H), 3.94–3.86 (m, 2H), 2.04 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.1, 169.9, 169.8, 169.2, 162.0, 136.2, 136.1, 134.1, 129.9, 128.2, 124.0, 121.3, 101.0, 70.6, 70.4, 68.4, 67.2, 66.8, 63.0, 61.0, 20.4 (3C), 20.3; IR (neat NaCl) cm^{-1}: 3132, 2929, 1748, 1734, 1696, 1652, 1556; HRMS m/z calcd $C_{26}H_{31}N_2O_{12}$ $[M+H]^+$: 563.1872; found: 563.1867; $[\alpha]_D^{25}$ −10.4 (c 1.6 in $CHCl_3$).

5.1.2.11. (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-2-hydroxyethyl isocyanoacetate (10). To a solution of **7** (0.38 mmol, 180 mg) in DCM (2.0 mL) were added Et_3N (1.14 mmol) and $POCl_3$ (0.38 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C for 2 h and saturated $NaHCO_3$ was added. The mixture was extracted three times with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography using 20% ether in DCM as an eluent affording 101 mg (58%) of **10**. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.34 (dd, 1H, J=3.5, 1.0 Hz), 5.15 (dd, 1H, J=10.5, 8.0 Hz), 4.97 (dd, 1H, J=10.5, 3.5 Hz), 4.50 (d, 1H, J=8.0 Hz), 4.34 (t, 2H, J=5.0 Hz), 4.25 (s, 2H), 4.16–3.75 (m, 5H), 3.77–3.70 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.2, 170.0, 169.9, 169.3, 163.8, 161.2, 100.9, 70.6, 70.5, 68.4, 66.8, 66.4, 65.0, 61.1, 43.2, 20.6, 20.5 (2C), 20.4; IR (neat NaCl) cm^{-1}: 2923, 2165, 1749, 1734, 1652, 1556; HRMS m/z calcd $C_{19}H_{26}N_2O_{12}$ $[M+H]^+$: 460.1450; found: 460.1444; $[\alpha]_D^{25}$ −6.1 (c 1.5 in $CHCl_3$).

5.1.2.12. 4-[2-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy)ethoxycarbonyl]-1-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)phenyl]imidazole (11). To a solution of **5** (0.18 mmol) in DCM (2.0 mL) was added Et_3N

(0.54 mmol) and $POCl_3$ (0.18 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C until disappearance of the starting material. After this time, the mixture was filtered over silica gel using DCM/Et_2O (4/1) and concentrated under reduced pressure. The crude residue was dissolved in THF (2.0 mL) and isocyanide **10** (0.18 mmol) was added followed by Cu_2O (0.02 mmol) and proline (0.04 mmol). The resulting solution was stirred at room temperature until completion of the reaction. The crude residue was purified by flash column chromatography using pure ethyl acetate as an eluent. Compound **11** was obtained as a colorless oil (86 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.91 (d, 1H, J=1.0 Hz), 7.79 (d, 1H, J=1.0 Hz), 7.36 (d, 2H, J=9.0 Hz), 7.14 (d, 2H, J=9.0 Hz), 5.50 (dd, 1H, J=10.5, 8.0 Hz), 5.47 (d, 1H, J=3.0 Hz), 5.37 (d, 1H, J=3.0 Hz), 5.21 (dd, 1H, J=10.5, 8.0 Hz), 5.13 (dd, 1H, J=10.5, 3.5 Hz), 5.09 (d, 1H, J=7.5 Hz), 4.99 (dd, 1H, J=10.5, 3.5 Hz), 4.62 (dd, 1H, J=8.0 Hz), 4.54–4.42 (m, 2H), 4.26–4.09 (m, 6H), 4.00–3.91 (m, 2H), 2.19 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.2 (2C), 170.1 (2C), 170.0, 169.5, 169.3, 162.2, 156.6, 136.6, 134.4, 131.7, 124.6, 123.3, 118.2, 101.2, 99.4, 71.1, 70.8, 70.6 (2C), 68.6, 68.4, 67.4, 67.0, 66.7, 63.3, 61.2 (2C), 20.7, 20.6 (6C), 20.5; IR (neat NaCl) cm^{-1}: 3021, 2924, 1744, 1739, 1652, 1556, 1222; HRMS m/z calcd $C_{40}H_{49}N_2O_{22}$ $[M+H]^+$: 909.2772; found: 909.2764; $[\alpha]_D^{25}$ −3.6 (c 1.4 in $CHCl_3$).

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) for a Canadian Research Chair in Therapeutic Chemistry to R.R.

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