Pergamon

Tetrahedron Letters 43 (2002) 241–244

TETRAHEDRON LETTERS

Reactivity of 1,1′-thiocarbonyldiimidazole with glycosides: a novel and efficient glycosidic activation

Solen Josse,[a] Julien Le Gal,[a] Muriel Pipelier,[a] Jean-Paul Pradère,[a] Rachid Benhida[b] and Didier Dubreuil[a,*]

[a]*Laboratoire de Synthèse Organique associé au CNRS, UMR 6513, Faculté des Sciences et des Techniques, 2, rue de la Houssinière, BP 92208, F-44322 Nantes Cedex 3, France*

[b]*Laboratoire de Chimie Bioorganique UMR 6001, Université de Nice-Sophia Antipolis-Parc Valrose, F-06108 Nice Cedex 2, France*

Received 8 October 2001; revised 6 November 2001; accepted 7 November 2001

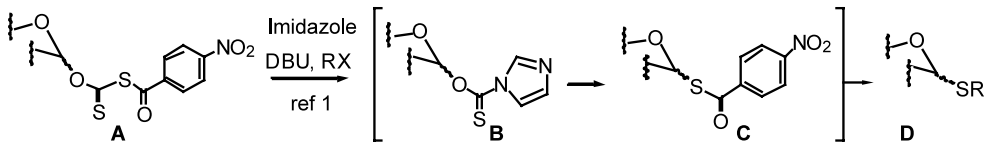
Abstract—The synthesis of monoglycosyl imidazoles and 1,1′-di-*O*-glycosides is described by direct glycosylation process from reducing sugar in the presence of 1,1′-thiocarbonyldiimidazole. Novel anomeric groups as 1-*O*-(imidazolyl)thiocarbonyl and 1-*O*-(imidazolyl)carbonyl are presented as potent glycosidic activators. © 2002 Elsevier Science Ltd. All rights reserved.

In continuation of studies on novel glycosylation processes using sulfur carbonyl chemistry, we have devised a direct access to thioglycoside derivatives **D** from 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl glycoside **A** avoiding the use of osidic catalysts (Scheme 1).[1]

The rearrangement pathway proposed for the in situ transformation of the anomeric *p*-nitrobenzoylxanthate group **A** into the thioester glycoside intermediate **C** involves the activation of the glycoside by an (imidazolyl)thiocarbonyl group **B**. In order to confirm the efficiency of (imidazolyl)thiocarbonyl as glycosidic activator, the reactivity of the 1,1′-thiocarbonyldiimidazole at the reductive position of sugars has been investigated. A novel direct synthesis of 1-*N*-(imidazolyl)glycosyls and 1,1′-di-*O*-glycosides, under mild and neutral conditions, was thus designed.

The glycosidic activation was firstly evaluated in the furanose series. The treatment of the 2,3,5-tri-*O*-benzyl-D-ribofuranose **1** with 1,1′-thiocarbonyldiimidazole (1.1 equiv.) in 1,2-dichloroethane (1,2-DCE) solvent (rt, 12 h) afforded the *N*-(α,β-D-ribofuranosyl)imidazole **3**[2] and the 1,1′-di-*O*-riboside **4**, in 50 and 20% yield, respectively (Scheme 2). The purification by flash chromatography on silica gel allowed to isolate the anomers **3α** and **3β** in 6/4 ratio. The diastereoisomer **4α,α**[3] was also purified from the anomeric mixture of the di-*O*-riboside **4** in 60% yield. In contrast to previous work on the synthesis of (ribosyl)imidazole using silyl Hilbert–Johnson–Vorbrugen method, we did not observe the formation of the corresponding di-*N*-ribosyl imidazolium salt.[4] These results emphasises the ability of (imidazolyl)thiocarbonyl group to be a potent glycosidic activator but raised the question of the reaction mechanism. The prior formation of anomers **2** was clearly observed on TLC after 30 min of experiment and their structures were assigned by ^{1}H, ^{13}C NMR and IR analysis.[5]

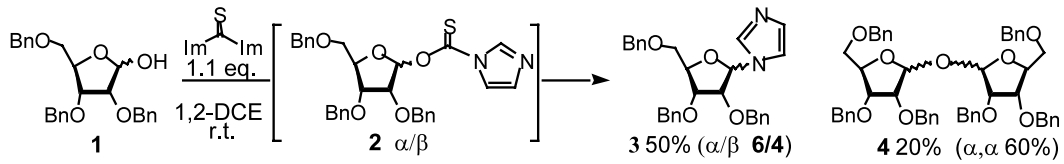
The (imidazolyl)thiocarbonyl ribosides **2** were isolated only in small amount because during concentration of the reaction mixture in vacuo, they are converted into



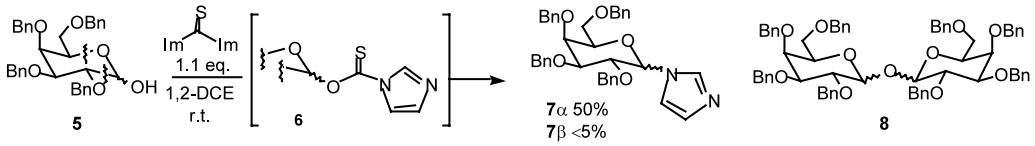
Scheme 1.

* Corresponding author. Tel.: 33 (0)2 51 12 54 20; e-mail: dubreuil@chimie.univ-nantes.fr

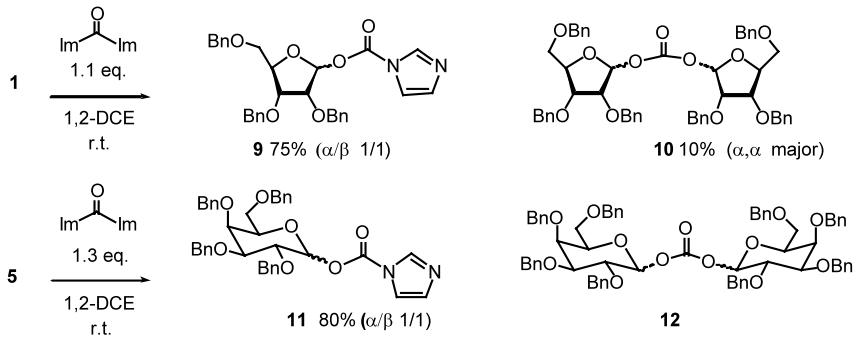
PII: S0040-4039(01)02123-2



Scheme 2.



Scheme 3.



Scheme 4.

compounds **3** and **4**. However, the yield in the (ribofuranosyl)imidazole products clearly shows that intermediates **2** were formed at least in 80% yield. Therefore, their stability in the reaction medium suggests that they should be quenched in the presence of other nucleophiles, as glycosidic acceptors.

Under the same conditions (thiocarbonyldiimidazole 1.1 equiv., 1,2-DCE, rt) the 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose **5** afforded the protected *N*-(α-D-galactopyranosyl)imidazole **7α**[6] as major monoglycosyl product in 50% yield (Scheme 3).

As it is admitted that glycosyl imidazole derivatives do not equilibrate,[7] the occurrence of an oxocarbonium intermediate seems to be not operating in this direct glycosylation process and a SN_2 mechanism appears more probable. The presence of the anomer **7β** in less than 5% yield emphasises the relative instability of the intermediate **6α**. This observation correlates with the fact that (imidazolyl)thiocarbonyl galactosides **6** are not observable either by TLC or ^1H, ^{13}C NMR control.

In order to evaluate the reactivity of the thiocarbonyldiimidazole, complementary experiments were performed on sugars **1** and **5** in the presence of 1,1′-carbonyldiimidazole (Scheme 4).

The treatment at room temperature of the ribofuranose **1** with 1.1 equiv. of 1,1′-carbonyldiimidazole in 1,2-dichloroethane solvent, afforded, after only 1 h of stirring, the *O*-(imidazolyl)carbonyl ribofuranoside **9**[8] in 75% yield (α/β ratio = 1/1) and an anomeric mixture of the carbonyl di-*O*-riboside **10** (10%). Under the same condition, the galactopyranose **5** furnished the corresponding *O*-(imidazolyl)carbonyl galactoside **11**[9] in 80% yield (α/β ratio = 1/1) with trace of the di-*O*-galactoside **12**.

In conclusion, furanose and pyranose precursors react with 1,1′-thiocarbonyldiimidazole to produce monoglycosyl imidazole derivatives by direct *N*-glycosylation process under mild and neutral conditions. The influence of the experimental conditions (solvent, temperature, stoichiometry, protecting groups,...) on the reaction is under evaluation. However, (imidazolyl)thiocarbonyl and (imidazolyl)carbonyl are now prone to be candidates as efficient glycoside activators. Their use in *O*- and *N*-glycosylation, is under way in our laboratory like it was already performed for *S*-thioglycosylation.[1] The synthesis of substituted and unsymmetrical thiocarbonyl azaheterocycle reagents is also under progress for the access to highly substituted nucleosides and glycosides by direct glycosylation process.

References

1. Josse, S.; Le Gal, J.; Pipelier, M.; Cléophax, J.; Olesker, A.; Pradère, J.-P.; Dubreuil, D. *Tetrahedron Lett*. **2002**, *43*, 237–239.

2. ***N*-(2,3,4-Tri-*O*-benzyl-α,β-D-ribofuranosyl)imidazole 3**:
α-Anomer: An NOE effect was observed between H_1 and H_2. ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.54 (dd, 1H, H_{5a}, $^2J_{5a-5b}=10.8$, $^3J_{5a-4}=3.2$); 3.59 (dd, 1H, H_{5b}, $^2J_{5a-5b}=10.8$, $^3J_{5b-4}=3.2$); 4.14 (m, 1H, H_3); 4.25 (t, 1H, H_2, $^3J_{2-1}=^3J_{2-3}=5.3$); 4.32 (m, 2H, CH_2(OBn)); 4.36 (m, 1H, H_4); 4.44–4.55 (m, 3H, CH_2(OBn)); 4.66 (d, 1H, CH_2(OBn), $^2J=11.6$); 5.83 (d, 1H, H_1, $^3J_{1-2}=5.3$); 7.05 (br s, 1H, H(Imid)); 7.11–7.13 (m, 1H, CH(OBn)); 7.24–7.36 (m, 15H, 14 CH(OBn), H(Imid)); 7.78 (br s, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 69.8 (C_5); 73.0, 73.2, 73.7 (3 CH_2(OBn)); 76.9 (C_3); 77.6 (C_2); 82.2 (C_4); 86.2 (C_1); 119.3 (CH(Imid)); 127.7–128.5 (CH(OBn)); 128.9 (CH(Imid)); 137.0 (CH(Imid)); 137.6–137.8 (Cq(OBn)). MS (CI) (NH_3) $[M+H]^+=471$.
β-Anomer: An NOE effect was observed between H_1 and H_4). ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.51 (dd, 1H, H_{5a}, $^2J_{5a-5b}=10.6$, $^3J_{5a-4}=3.0$); 3.66 (dd, 1H, H_{5b}, $^2J_{5a-5b}=10.6$, $^3J_{5b-4}=3.0$); 4.05 (m, 1H, H_3); 4.10 (t, 1H, H_2, $^3J_{2-1}=^3J_{2-3}=5.9$); 4.31 (m, 1H, H_4); 4.39–4.64 (m, 6H, CH_2(OBn)); 5.77 (d, 1H, H_1, $^3J_{1-2}=5.9$); 6.99 (br s, 1H, H(Imid)); 7.02 (br s, 1H, H(Imid)); 7.14–7.36 (m, 15H, CH(OBn)); 7.62 (br s, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 69.9 (C_5); 72.4, 72.8, 73.7 (CH_2(OBn)); 76.8 (C_3); 81.8 (C_2); 82.4 (C_4); 88.9 (C_1); 116.5 (CH(Imid)); 127.8–128.6 (CH(OBn)); 129.9 (CH(Imid)); 136.2 (CH(Imid)); 137.0–137.5 (Cq(OBn)). MS (CI) (NH_3) $[M+H]^+=471$.
See also: (a) James, M. N. G.; Matsushima, M. *Acta Crystallogr*. **1972**, *B29*, 838–846; (b) Miles, D. W.; Revandar, G. R.; Robins, R. K. *J. Phys. Chem*. **1983**, *87*, 2444–2450; (c) Mitra, C.; Saran, A.; Govil, G. *Ind. J. Chem*. **1978**, *16B*, 132–136.
3. **1,1′-Di-*O*-(2,3,4-tri-*O*-benzyl)-α,α-D-riboside 4**: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.51 (dd, 1H, H_{5a}, $^2J_{5a-5b}=11.1$, $^3J_{5a-4}=3.5$); 3.65 (dd, 1H, H_{5b}, $^2J_{5a-5b}=11.1$, $^3J_{5b-4}=2.3$); 4.12–4.15 (m, 1H, H_3); 4.20 (m, 1H, H_2); 4.31–4.33 (m, 1H, H_4); 4.37 (d, 1H, CH_2(OBn), $^2J=11.7$); 4.48 (t, 2H, CH_2(OBn), $^2J=12.6$); 4.54 (d, 1H, CH_2(OBn), $^2J=12.2$); 4.71 (d, 1H, CH_2(OBn), $^2J=12.1$); 4.84 (d, 1H, CH_2(OBn), $^2J=12.1$); 6.41 (br s, 1H, H_1); 7.24–7.39 (m, 15H, CH(OBn)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 69.0 (C_5); 72.3, 72.6, 73.6 (CH_2(OBn)); 77.2 (C_3); 81.0 (C_2); 81.9 (C_4); 90.9 (C_1); 127.7, 128.0, 128.3, 128.5, 128.5, 128.6 (CH(OBn)); 137.6, 137.7, 138.2 (Cq(OBn)).
4. Al Mourabit, A.; Beckmann, M.; Poupat, C.; Ahond, A.; Potier, P. *Tetrahedron: Asymmetry* **1996**, *12*, 3455–3464.
5. ***N*-(2,3,4-Tri-*O*-benzyl-α,β-D-ribofuranosyl)imidazolylthiocarbonyl 2**:
α-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.55 (dd, 1H, H_{5a}, $^2J_{5a-5b}=11.1$, $^3J_{5a-4}=3.2$); 3.71 (dd, 1H, H_{5b}, $^2J_{5a-5b}=11.1$, $^3J_{5b-4}=2.6$); 4.06 (d, 1H, H_2, $^3J_{2-3}=4.5$); 4.28 (dd, 1H, H_3, $^3J_{2-3}=4.5$, $^3J_{3-4}=7.3$); 4.42–4.46 (m, 4H, H_4, CH_2(OBn)); 4.56 (d, 1H, CH_2(OBn), $^2J=12.1$); 4.67–4.75 (d, 1H, CH_2(OBn), $^2J=12.1$); 6.32 (br s, 1H, H_1); 6.95 (br s, 1H, H(Imid)); 7.16–7.43 (m, 16H, H(Imid), CH(OBn)); 7.95 (br s, 1H, H(Imid)). ^{13}C NMR† ($CDCl_3$, 100 MHz): δ 69.9 (C_5); 72.7, 72.9, 73.5 (CH_2(OBn)); 76.2 (C_3); 78.9 (C_2); 82.6 (C_4); 102.6 (C_1); 117.2 (CH(Imid)); 127.7, 128.0, 128.3, 128.6 (CH(OBn)); 130.8 (CH(Imid)); 137.2, 137.3, 137.8 (Cq(OBn)); 147.3 (CH(Imid)). IR (NaCl) ν (cm^{-1}): 1762 (CS).
β-Anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.40 (d, 1H, H_1, $^3J_{1-2}=4$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.6 (C_1).
6. ***N*-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-galactopyranosyl)imidazole 7**:
α-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.55–3.64 (m, 3H, H_{6a}, H_{6b}, H_5 or H_4); 3.90–3.93 (m, 1H, H_3); 3.97 (m, 1H, H_5 or H_4); 4.29–4.31 (m, 1H, H_2); 4.38–4.90 (m, 8H, CH_2(OBn)); 5.74 (d, 1H, H_1, $^3J_{1-2}=4.4$); 7.04 (m, 1H, H(Imid); 7.15 (m, 1H, H(Imid)); 7.17–7.32 (m, 20H, CH(OBn)); 7.91 (m, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 67.9 (C_6); 72.1 (C_5 or C_4); 73.3 (CH_2(OBn)); 73.5 (CH_2(OBn)); 74.4 (C_5 or C_4); 74.8 (C_2); 77.8 (C_3); 81.5 (C_1); 118.6 (CH(Imid)); 127.8–129.0 (CH(OBn)); 129.9 (CH(Imid)); 137.2 (CH(Imid)); 137.6, 137.9, 138.1, 138.3 (Cq(OBn)). mp 110–112°C. MS (CI) (NH_3) $[M+H]^+=591$.
β-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.60 (m, 2H, H_{6a}, H_{6b}); 3.65 (dd, 1H, H_3, $^3J_{3-4}=2.6$, $^3J_{3-2}=9.0$); 3.73 (t, 1H, H_5, $^3J_{5-6a}=^3J_{5-6b}=6.0$); 3.91 (d, 1H, CH_2(OBn), $^2J=10.1$); 4.00–4.05 (m, 2H, H_2, H_4); 4.44 (d, 2H, CH_2(OBn), $^2J=8.8$); 4.51 (d, 1H, CH_2(OBn), $^2J=10.1$); 4.62 (d, 1H, CH_2(OBn), $^2J=11.5$); 4.75 (m, 2H, CH_2(OBn)); 4.98 (d, 1H, CH_2(OBn), $^2J=11.5$); 5.03 (d, 1H, H_1, $^3J_{1-2}=8.7$); 7.02 (m, 2H, CH(OBn)); 7.11 (br s, 1H, CH(Imid)); 7.15 (br s, 1H, CH(Imid)); 7.23–7.36 (m, 18H, CH(OBn)); 7.71 (br s, 1H, CH(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.5 (C_6); 72.9 (CH_2(OBn)); 73.6 (C_2); 73.8 (CH_2(OBn)); 74.9, 75.6 (CH_2(OBn)); 76.4 (C_5); 79.3 (C_4); 82.9 (C_3); 86.3 (C_1); 117.2 (CH(Imid)); 127.7–128.6 (CH(OBn)); 129.8 (CH(Imid)); 136.8 (CH(Imid)); 137.3, 137.7, 138.1, 138.6 (Cq(OBn)).
7. (a) Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, K. B. *J. Am. Chem. Soc*. **1999**, *121*, 6911–6918; (b) Fabian, M. A.; Perrin, C. L.; Sinnot, M. L. *J. Am. Chem. Soc*. **1994**, *116*, 8398–8399.
8. ***N*-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-ribofuranosyl)imidazolylcarbonyl 9**:
α-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.57 (dd, 1H, H_{5a}, $^2J_{5a-5b}=11.1$, $^3J_{5a-4}=3.4$); 3.70 (dd, 1H, H_{5b}, $^2J_{5a-5b}=11.1$, $^3J_{5b-4}=2.8$); 4.08 (d, 1H, H_2, $^3J_{2-3}=4.6$); 4.30 (dd, 1H, H_3, $^3J_{3-2}=4.6$, $^3J_{3-4}=7.5$); 4.42–4.77 (m, 7H, H_4, CH_2(OBn)); 6.33 (br s, 1H, H_1); 6.94 (br s, 1H, H(Imid)); 7.07–7.37 (m, 16H, H(Imid), CH(OBn)); 7.95 (br s, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.7 (C_5); 72.7, 72.8, 73.5 (CH_2(OBn)); 76.1 (C_3); 78.9 (C_2); 82.6 (C_4); 102.5 (C_1); 117.1 (CH(Imid)); 127.7–128.6 (CH(OBn)); 130.7, 137.1 (CH(Imid)); 137.7, 137.6, 137.8 (Cq(OBn)).
β-Anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.40 (d, 1H, H_1, $^3J_{1-2}=4.1$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.7 (C_1).
9. ***N*-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-galactopyranosyl)imidazolylcarbonyl 11**:
α-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.53–3.61 (m, 2H, H_6); 3.87 (dd, 1H, H_3, $J=2.0$, $J=10.0$); 4.02 (t, 1H, H_5, $J=7.0$); 4.07 (br s, 1H, H_4); 4.25 (dd, 1H, H_2, $J=3.0$, $J=10.0$); 4.43 (m, 2H, CH_2(OBn)); 4.58 (d, 1H, CH_2(OBn), $J=11.0$); 4.73–4.82 (m, 4H, $2CH_2$(OBn)); 4.96 (d, 1H, CH_2(OBn), $J=11.0$); 6.43 (d, 1H, H_1, $J=3.0$); 7.09 (br s, 1H, H(Imid)); 7.25–7.36 (m, 21H, 20CH(OBn), H(Imid)); 8.07 (br s, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.2 (C_6); 73.1 (CH_2(OBn), C_5); 73.9 ($2CH_2$(OBn)); 74.3 (C_4); 75.1 (CH_2(OBn), C_2); 78.1 (C_3); 96.0 (C_1); 117.4 (CH(Imid)); 127.8–128.6 (CH-(OBn)); 130.9 (CH(Imid)); 137.3 (CH(Imid)); 137.8–138.4 (Cq(OBn)); 147.5 (CO). IR (NaCl) ν (cm^{-1}): 1768 (CO).

† δ (chemical shifts) in ppm and *J* (coupling constants) in Hz.

β-Anomer: ^{1}H NMR† ($CDCl_3$, 400 MHz): δ 3.59 (m, 2H, H_6); 3.68 (dd, 1H, H_3, $^{3}J_{3-4}=1.8$, $^{3}J_{2-3}=9.5$); 3.76 (t, 1H, H_5, $^{3}J_{5-6}=6.3$); 4.00 (br s, 1H, H_4); 4.07 (t, 1H, H_2, $J=8.8$); 4.39, 4.46 (2d, 2H, CH_2(OBn), $^{2}J=11.4$); 4.69–4.78 (m, 4H, 2CH_2(OBn)); 4.86, 4.93 (2d, 2H, CH_2(OBn), $^{2}J=11.4$); 5.71 (d, 1H, H_1, $J=7.9$); 7.03 (br s, 1H, H(Imid)); 7.21–7.36 (m, 21H, CH(Imid), CH(OBn)); 7.98 (br s, 1H, H(Imid)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.0 (C_6); 73.0 (CH_2(OBn)); 73.1 (C_4); 73.7 (CH_2(OBn)); 74.7 (C_5); 75.0, 75.5 (CH_2(OBn)); 77.3 (C_2); 82.6 (C_3); 97.5 (C_1); 117.3 (CH(Imid)); 127.8–128.7 (CH(OBn)); 130.9 (CH(Imid)); 137.4 (CH(Imid)); 137.7, 137.8, 138.0, 138.3 (Cq(OBn)); 147.4 (CO). IR (NaCl) ν (cm^{-1}): 1773 (CO).