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Investigation of benzoyloximes as benzoylating reagents: benzoyl-Oxyma as a selective benzoylating reagent†

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Hydroxybenzotriazole (HOBT) and HOBT-derived reagents have been classified as Class I explosives, with restrictions on their transportation and storage. We explored a range of benzoylated oxime-based reagents as alternatives to benzoyloxybenzotriazole (BBTZ) for the selective benzoylation of carbohydrate polyols. Benzoylated oximes derived from 2-hydroximino-malononitrile, ethyl 2-hydroximino-2-cyanoacetate (Oxyma), and *tert*-butyl 2-hydroximino-2-cyanoacetate were most effective for benzoylation of a simple primary alcohol, with yields approaching that obtained for BBTZ. When applied to carbohydrate diols, the most effective reagent was identified as benzoyl-Oxyma. Benzoyl-Oxyma is a highly crystalline, readily prepared alternative to BBTZ, useful in the selective benzoylation of carbohydrate polyols.

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Introduction

Benzoic acid esters are widely used hydroxyl protecting groups for polyhydroxylated substrates such as nucleosides, sugars, and inositol owing to their ease of introduction and removal, and their stability to a wide range of reaction conditions.^{1,2} In the context of carbohydrate chemistry, benzoates can be used to alter stereoselectivity of glycosylations by providing anomic assistance,³ and to attenuate reactivity according to the armed/disarmed principle.⁴ The selective benzoylation of a polyol⁵ can be achieved by careful control of reaction conditions⁶ and through use of a range of selective benzoylating reagents including benzoyl cyanide,^{7,8} *N*-benzoyltetrazole,^{9–11} *N*-benzoylimidazole,^{9,10,12} Mitsunobu conditions,¹³ benzoyl chloride/collidine,¹⁴ and BzCl in combination with organotin reagents.¹⁵ However, depending on the substrate or reagent, various problems emerge including poor solubility for many polyol substrates at the low temperatures sometimes required, high toxicity, poor reactivity, and/or poor regioselectivity. Among the most reliable and widely-used selective benzoylating reagent is the hydroxybenzotriazole (HOBT; 1) derived benzoyloxybenzotriazole (BBTZ; 2), first introduced for this purpose by Kim and co-workers (Fig. 1).¹⁶ BBTZ reacts under mild conditions with outstanding regio- and chemoselectivity

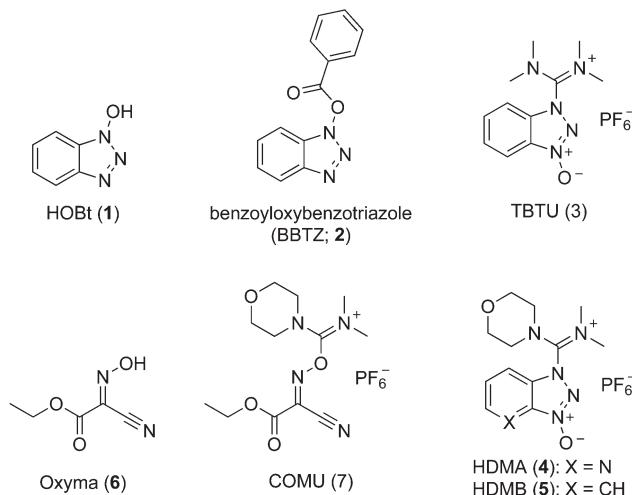


Fig. 1 Benzotriazole- and Oxyma-based reagents.

that surpasses that of most other benzoylating reagents.¹⁷ The intrinsically high regioselectivity of benzoylation with BBTZ has been harnessed in the use of BzOH with the HOBT-derived ammonium salt TBTU (3),¹⁸ which ostensibly proceeds through a BBTZ intermediate.

In recent years, the safety of HOBT has been called into question. HOBT and its monohydrate are classified as Class 1 explosives, with significant limitations on their transport and storage.¹⁹ Safety concerns extend to HOBT-derivatives such as TBTU (3),¹⁹ HDMA (4)²⁰ and HDMB (5) (Fig. 1).²⁰ Against this backdrop, various oxime-based alternatives have emerged as

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viable alternatives to HOBr as nucleophilic catalysts in peptide couplings. In particular ethyl 2-hydroximino-2-cyanoacetate (Oxyma, OxymaPure, **6**) has been identified as a viable alternative to HOBr,²¹ and has been elaborated to the uronium-type coupling reagent COMU (**7**)^{20,22} which is effective for both peptide couplings²⁰ and esterifications.^{18,23} Both Oxyma and COMU show a better safety profile than HOBr and HOBr-based reagents, including a lower heatflow associated with smaller increases in temperature and lower released pressures, equating to a lower risk of runaway thermal explosions.^{20,21} In this work we report the synthesis of a range of benzoylated oximes and investigation of their ability to act as selective benzoylating reagents. Benzoyl-Oxyma is identified as a readily synthesized, highly crystalline and storable alternative for BBTZ in the regio- and chemoselective acylation of carbohydrate alcohols.

Results and discussion

Design and synthesis of oxime-based benzoylating reagents

Initially we sought to explore a range of benzoylated oxime-based reagents varying in the nature of the electron-withdrawing groups adjacent to the oxime. It has been found that Oxyma (**6**) can undergo side-reactions at the ethoxycarbonyl group.^{21,24} Therefore we also studied the *tert*-butyl ester **8** (derived from *tert*-butyl cyanoacetate)²⁵ and the bis-nitrile **9** (derived from malonitrile)²⁶ (Table 1). In order to complete the series we included the bis-ethoxycarbonyl derivative **10** (derived from diethyl malonate).²⁷ Several analogues of COMU have been reported to provide improved peptide couplings, most notably based on oximes **11** (derived from Meldrum's acid)²⁸ and **12** (derived from dimethylbarbituric acid),²⁹ which were also included in our studies. Oximes **6**, **10–12** or the corresponding silver salts of **8** and **9**, were converted to benzoylated derivatives **13**, **14**, **15**,²⁶ **16**,³⁰ **17** and **18** by treatment with benzoic anhydride (Bz_2O) in ether, or using $BzCl$ and pyridine or Et_3N . Among these examples, we highlight the exceptionally simple preparation of benzoyl-Oxyma (**13**): addition of Bz_2O to a 0.3 M solution of Oxyma in Et_2O resulted in the formation of a precipitate within 1 min. Filtration and drying provided the pure reagent. This result stands in contrast with the preparation of BBTZ (**2**): commercial HOBr containing 20% water can either be dried under vacuum (caution: explosion risk) or alternatively stirred with activated molecular sieves, prior to reaction with $BzCl$ and Et_3N .¹⁶ Following aqueous workup, the reagent may, with some difficulty, be crystallized from $EtOAc$ /petrol, with the crystallization likely complicated by the known interconversion of *O*- and *N*-acyl isomers.³¹ In the case of the esters **13** and **14** derived from unsymmetrical oximes, the stereochemistry about the oxime double bond was defined as *Z* by single crystal X-ray diffraction analysis (Fig. 2).

While simple oximes possess pK_a values of 8.3–11.8,³³ Oxyma (**6**) is characterized by the presence of strongly electron-withdrawing cyano and ethoxycarbonyl groups. The pK_a value of Oxyma is reported to be 4.6,³⁴ matching that reported for HOBr (**1**).³⁵ In order to understand the leaving group ability of

Table 1 Oximes and their benzylated derivatives. pK_a values and preparation

Oxime	pK_a value	Benzoyl-oxime	Method ^a	Yield (%)
6	4.32	13	A	90
8	4.39	14	C	65
9	4.09 ³²	15	C	64
10	4.32	16	D	78
11	3.96	17	D	80
12	4.46	18	B	83

^a Method A: Bz_2O , Et_3N , Et_2O ; method B: Bz_2O , Et_3N , CH_2Cl_2 ; method C: $BzCl$, pyr, CH_2Cl_2 ; method D: $BzCl$, Et_3N , CH_2Cl_2 .

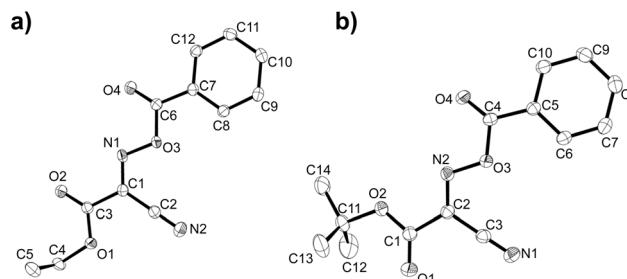


Fig. 2 ORTEP representations of the molecular structures of benzoylated oximes (a) **13** and (b) **14**, determined by single-crystal X-ray crystallography. Ellipsoids are at the 50% probability level.

various oximes we initially sought to extract pK_a data from the literature; however, owing to the range of different solvents used for these studies we were unable to directly compare the various oximes. Consequently, we measured the pK_a values for the series of compounds by spectrophotometric titration of the oximes in a solution in 95% MeCN in water.³² As revealed in Table 1, the pK_a values for the series of oximes fell within the



Table 2 Comparison of benzoylation of 4-phenylbenzyl alcohol (**19**) by BBTZ and various benzoyl oximes

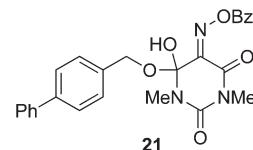
Entry	Reagent	Yield ^a (%)
1	BBTZ (2)	100
2	Benzoyl-Oxyma (13)	80 (95) ^b
3	14	98
4	15	95
5	16	50 ^c
6	17	2
7	18	15

^a Reactions performed using Et₃N as received. ^b Reaction using Et₃N dried by distillation over CaH₂. ^c Yield after 5 days. At this time the reaction still contained unreacted **4** and **19**.

range 3.96–4.39, and under these conditions the p_{K_a} value of HOBt was determined to be 4.25; based on their p_{K_a} values, the series of oximes possess similar intrinsic leaving group ability.

Investigation of the benzoylation of a simple primary alcohol

The effectiveness of the benzoylated oximes as benzoylating agents was investigated by studying their reaction with a simple alcohol, 4-phenylbenzyl alcohol **19** (Table 2). This substrate was chosen as it is crystalline, easily dried and readily detected owing to the presence of a chromophore. Treatment of **19** with 1.1 equiv. of BBTZ (2) and Et₃N at 0 °C and warming to room temperature overnight afforded the benzoate **20** in quantitative yield (entry 1), highlighting the impressive benzoylating ability of this reagent. Treatment with 1.1 equiv. of the nitrile-containing reagents **13–15** gave yields of 95–98% (entries 2–4). Significantly, we found that for optimal yields using benzoyl-Oxyma **13**, use of dry Et₃N was critical, as using undried Et₃N only afforded an 80% yield. This sensitivity to trace moisture appears to be unique to the Oxyma-derived reagent as close to quantitative yields were obtained with the *t*-butyl ester **14**, dicyanooxime **15** and BBTZ using undried Et₃N, results that suggest that the carbonyl group of the Oxyma-derived **13** may be a site of unwanted reactivity. On the other hand the malonate-derived reagents **10–12** gave much poorer yields. The diethyl malonate derivative **10** provided just 50% after 5 d, with tlc evidence of both unreacted **10** and **19** (entry 5); the Meldrum's acid derivative **11** delivering only 2% (entry 6), accompanied by degradation of the reagent to materials that could not be identified; and the barbiturate **12** providing only a 15% yield (entry 7). In the last case, the major by-product was tentatively assigned as the addition product **21**. Overall, these results reveal that despite similarity in the p_{K_a} value of the conjugate acid of the leaving group, significant differences in reactivity occur across the series.



Securing exclusive nucleophilic attack at the carbonyl of the oxime-ester for these reagents, which contain multiple electrophilic sites at the oxime imino group and the adjacent nitrile/ester positions, is critical for high-yielding benzoylation. The isolation of the adduct **21** provides an indication of one of the alternative modes of reactivity. Despite considerable effort, we were unable to convincingly identify any by-products derived from reaction at the ethoxycarbonyl group of **13**. El-Fahem, Albericio and coworkers demonstrated that Oxyma undergoes reaction at the imino and ethoxycarbonyl groups when used as an additive in peptide coupling.²¹ In the case of the Meldrum's acid derived **17**, tlc analysis revealed rapid consumption of the reagent yet little product formation, and it appears likely that nucleophilic attack at the dioxanedione carbonyl groups results in fragmentation of the reagent. The poor reactivity of **16** is at odds with the p_{K_a} value of the conjugate acid of the leaving group; however, we highlight that this reagent is the only non-crystalline compound of the series and we speculate that the two ethoxycarbonyl groups α to the oxime cause steric distortion of the system, affecting its conjugation and attenuating its reactivity.

Selective benzoylation of carbohydrate alcohols

Having identified the nitrile-containing oximes **13–15** as the most effective benzoylating reagents for a simple alcohol, we next turned our attention to the selective acylation of carbohydrate diols. Typically, good acylation selectivity is observed for diols when one hydroxyl group has a *cis*-disposed vicinal

Table 3 Comparison of benzoylation of galactoside **22** (to the 3-benzoate **23**) and glucoside **24** (to the 2-benzoate **25**) by BBTZ and benzoyl oximes **13–15**

Entry	Substrate	Reagent	Yield ^a (%)
1	22	BBTZ	100
2	22	Benzoyl-Oxyma (13)	90 (100) ^b
3	22	14	90 (100) ^b
4	22	15	72 (90) ^b
5	24	BBTZ (1)	87
6	24	Benzoyl-Oxyma (13)	83 (89) ^b
7	24	14	75 (93) ^b
8	24	15	80 (93) ^b

^a Reactions were performed using 1.1 equivalent of reagent, 1.2 equiv. dry Et₃N in dry CH₂Cl₂, 0 °C to rt overnight. ^b Yield for reaction performed using 1.4 equiv. of benzoyl-Oxyma.



Table 4 Selective benzoylation of carbohydrate alcohols using benzoyl-Oxyma (13)

Entry	Substrate	Product	Equivalents of benzoyl-Oxyma	Yield ^a (%)
1			1.4	86
2			1.4	50
3			1.4	93
4			2.8	41
5			2.2	55

^a Reactions were performed using the indicated equivalent of reagent, 1.2-fold of dry Et₃N in dry CH₂Cl₂, 0 °C to rt overnight.

oxygen, which is believed to result from the presence of an intramolecular hydrogen bond that enhances the reactivity of the hydroxyl group. Using the optimum protocol identified from Table 2, the benzoylation of galactoside 22 was studied (Table 3). Consistent with literature yields³⁶ treatment of galactoside 22 with BBTZ provided a quantitative yield of the 3-benzoate 23 (entry 1). Among the three nitrile-based reagents, the best yield of 23 was obtained for the Oxyma-derived reagent 13 (90%, entry 2), which could be improved to a quantitative yield by using 1.4 equivalents of the reagent. We next explored acylation of the glucoside 24. BBTZ afforded 25 in an 87% yield (entry 5). The three nitrile-containing oximes 13–15 gave marginally lower yields, with the best result obtained for the Oxyma-derived reagent (83%, entry 6). Increasing the amount of the Oxyma-derived reagent to 1.4 equivalents provided 25 in an 89% yield, commensurate with that obtained using 1.1 equivalents of BBTZ. We therefore conclude that the nitrile-based reagents are effective for selective acylation of diols, with the Oxyma-derived reagent 13 the most promising. Although these reagents are slightly less effective than BBTZ, use of 1.4 equiv. of 13 provides similar yields to that obtained using 1.1 equiv. BBTZ.

In view of the importance of selective hydroxyl functionalization in carbohydrate chemistry, we explored several additional examples using benzoyl-Oxyma (13) (Table 4). Selectivity for a primary *versus* a secondary alcohol was demonstrated through the benzoylation of the 4,6-diol 26 to afford the 6-benzoate 27 in 86% yield (entry 1), the 2,6-diol 28 to afford the 6-benzoate 29 in 50% yield (entry 2), and the 2,4,6-triol 30 to afford the 6-benzoate 31 in 93% yield (entry 3), in each case using 1.4 equiv. of 13. Two additional transform-

ations are noteworthy. Treatment of 2,4,6-triol 30 with 2.8 equivalents of 13 afforded 2,6-dibenzoate 31 in 41%, with the greater reactivity of the 2-position relative to the 4-position a result of the *cis*-relationship with the anomeric oxygen. Finally, treatment of tetraol 33 with 2.2 equiv. of 13 directly provided the 3,6-dibenzoate 34 in 55% yield.

Conclusions

The classification of HOBT and related reagents as Class I explosives has provided an impetus for the development of new reagents that allow similar transformations with a lower risk of explosion. Oxime-based reagents, particularly those based on Oxyma, have emerged as effective alternatives for HOBT and have formed the basis of the development of COMU as a replacement for HBTU and HDMB. In this work we have explored a range of oxime-based alternatives to the selective acylating reagent BBTZ, leading to the identification of the nitrile-based benzoates 13–15 as the most promising representatives. In particular, benzoyl-Oxyma (13) can be considered a viable alternative to BBTZ, featuring a facile preparation, yields that approach those of BBTZ in various model reactions and a broad utility in the selective benzoylation of various carbohydrates.

Experimental

General

Proton nuclear magnetic resonance spectra (¹H NMR) and proton decoupled carbon nuclear magnetic resonance spectra



(^{13}C NMR) were obtained in deuterated chloroform, methanol- d_4 (CD_3OD) and $\text{DMSO}-d_6$ with residual protonated solvent as internal standard. Abbreviations for multiplicity are s, singlet; d, doublet; t, triplet; q, quartet; p, pentet. Flash chromatography was carried out on silica gel 60 according to the procedure of Still *et al.*³⁷ IR spectra were obtained as thin films or solids on a Fourier-transform attenuated total reflectance infrared spectrophotometer equipped with a diamond-coated zinc selenide sample accessory. Analytical thin layer chromatography (t.l.c.) was conducted on aluminium-backed 2 mm thick silica gel 60 GF_{254} and chromatograms were visualized with ceric ammonium molybdate (Hanessian's stain) or orcinol/ FeCl_3 (Bial's reagent). High resolution mass spectra (HRMS) were obtained by ionizing samples using electro-spray ionization (ESI) and a time-of-flight mass analyzer. Dry DMF was obtained by drying over 4 \AA molecular sieves. Hexanes refers to petroleum ether, boiling range 40–60 °C. CH_2Cl_2 and THF were dried over alumina according to the method of Pangborn *et al.*³⁸ Oxyma (ethyl 2-hydroximino-2-cyanoacetate, **6**) was purchased from Sigma-Aldrich. The synthesis of various oximes and oxime benzoates has been reported previously: **8**,²⁵ **9**,²⁶ **10**,²⁷ **11**,²⁸ **12**,²⁹ **15**,²⁶ and **16**.³⁰

Ethyl 2-benzoyloximino-2-cyanoacetate (benzoyl-Oxyma, **13**)

A mixture of benzoic anhydride (2.21 g, 8.44 mmol) and Oxyma (**6**) (1.00 g, 7.04 mmol) in dry diethyl ether (25 mL) was stirred at room temperature for 1 min. The resulting precipitate was filtered and washed with cold petroleum ether to afford **13** as a white crystalline powder (1.50 g, 90%), m.p. 99.3 °C (lit.³⁹ 100 °C); ^1H NMR (CDCl_3 , 400 MHz) δ 1.43 (3 H, t, *J* 7.1 Hz, CH_3), 4.50 (2 H, q, *J* 7.1 Hz, CH_2), 7.54–8.21 (5 H, m, Ph); ^{13}C NMR (CDCl_3 , 100 MHz) 14.1 (CH_3), 64.6 (CH_2), 107.1 (C=N), 125.8 (C≡N), 129.2, 130.6, 131.7, 135.2 (Ph), 157.0 (C=O), 160.7 (C=O); IR ν 2988.1, 2200.2, 1776.1, 1752.3, 1599.1, 1583.7, 1451.9, 1368.7, 1297.3, 1233.3, 1179.0, 1146.7, 1110.4, 1077.1, 1031.0, 996.2, 904.4, 837.5, 801.6, 764.9, 709.2, 666.5 cm^{-1} ; HRMS [M + Na]⁺ calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4\text{Na}$ *m/z* 269.0533, found 269.0532.

t-Butyl 2-benzoyloximino-2-cyanoacetate (**14**)

A solution of sodium nitrite (2.93 g, 42.5 mmol) in water (13 mL) was added to a solution of *t*-butyl cyanoacetate (2.00 g, 14.1 mmol) in acetic acid (6 mL) and water (6 mL) at 0 °C. The solution was stirred at room temperature for 12 h in the dark. A solution of AgNO_3 (2.40 g, 14.1 mmol) in water (13 mL) was added and stirred for 30 min. The resulting yellow precipitate was collected by filtration, washed with cold petroleum ether, and dried under vacuum (3.57 g, 70%). BzCl (0.554 g, 3.94 mmol) was added to a stirred solution of the yellow precipitate (1.00 g, 3.58 mmol) in toluene (7.5 mL). A drop of pyridine was added to the solution resulting in the rapid formation of a white precipitate. Stirring was continued for another 30 min and then the precipitate was collected by filtration. The filtrate was concentrated and the residue recrystallized to afford **14** as a white crystalline solid (0.62 g, 65%), m.p. 72.5–73.5 °C (ether/petroleum ether); ^1H NMR (CDCl_3 ,

400 MHz) δ 1.63 (9 H, s), 7.55–8.21 (5 H, m, Ph); ^{13}C NMR (CDCl_3 , 100 MHz) 27.0, 87.4, 107.4, 125.7, 128.9, 130.3, 132.6, 134.8, 155.2, 160.6; IR ν 3679.5, 2984.8, 2938.9, 2844.3, 2238.0, 1978.2, 1928.0, 1841.7, 1778.1, 1730.8, 1598.1, 1449.1, 1347.5, 1259.5, 1224.9, 1175.7, 1141.2, 1028.8, 989.8, 901.6, 843.0, 701.9, 665.7 cm^{-1} ; HRMS [M + Na]⁺ calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4\text{Na}$ *m/z* 297.0846, found 297.0847.

Benzoate ester of isonitroso Meldrum's acid (**17**)

Isonitroso Meldrum's acid **11**²⁸ (0.500 g, 2.89 mmol) was dissolved in CH_2Cl_2 (7 mL) and Et_3N (0.44 mL, 3.16 mmol) was added, followed by addition of BzCl (0.34 mL, 2.9 mmol). The solution was stirred for 1 h, then diluted with CH_2Cl_2 (35 mL) and stirred for another 5 min. The solution was washed with water (2 \times 20 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. Flash chromatography (5–10% EtOAc/petroleum ether) afforded **17** as a brown solid (1.50 g, 70%), m.p. 108.5–109 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 1.87 (6 H, s, CH_3), 7.55–8.27 (5 H, m, Ph); ^{13}C NMR (CDCl_3 , 100 MHz) 28.4, 46.0, 106.8, 126.2, 129.0, 129.2, 130.7, 131.0, 134.6, 135.1, 139.2, 150.9, 155.7, 161.3, 162.5; IR ν 3750.7, 2943.4, 1778.5, 1749.4, 1589.9, 1556.2, 1493.8, 1453.1, 1396.4, 1384.2, 1293.3, 1264.7, 1230.0, 1198.3, 1181.8, 1159.3, 1055.4, 1032.0, 1011.9, 982.3, 969.9, 949.0, 930.9, 891.0, 864.9, 798.8, 739.0, 701.8, 677.7, 667.1 cm^{-1} ; HRMS [M + Na]⁺ calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_6\text{Na}$ *m/z* 300.0479, found 297.0478.

Benzoate ester of isonitroso dimethylbarbituric acid (**18**)

Benzoic anhydride (0.70 g, 2.97 mmol) was added to a solution of isonitroso dimethylbarbituric acid **12**²⁹ (0.500 g, 2.70 mmol) in dry Et_2O (12.5 mL) and the solution was stirred overnight at room temperature. The resulting precipitate was filtered and washed with cold petroleum ether. The product was obtained as a green solid (0.65 g, 83%), m.p. 218.5–219 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 3.45 (3 H, s, CH_3), 3.47 (3 H, s, CH_3), 7.54–8.33 (5 H, m, Ph); ^{13}C NMR (CDCl_3 , 100 MHz) 29.0, 29.5, 31.0, 126.5, 129.1, 130.9, 134.9, 161.7; IR ν 3000.1, 1949.2, 1773.7, 1686.0, 1447.8, 1367.7, 1283.3, 1234.9, 1070.9, 1014.7, 994.2, 970.3, 924.2, 866.2, 793.4, 746.3, 716.5 cm^{-1} ; HRMS [M + Na]⁺ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_5\text{Na}$ *m/z* 312.0591, found 312.0595.

Protocol for benzoylation of 4-phenylbenzyl alcohol (**19**)

A mixture of 4-phenylbenzyl alcohol (**19**) (0.100 g, 0.542 mmol), 1.1 equivalents of the benzoylating reagent and Et_3N (0.091 mL, 0.650 mmol) in dry CH_2Cl_2 (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH_2Cl_2 , washed with water (2 \times 20 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10–15% EtOAc/petroleum ether) to afford 4-phenylbenzyl benzoate **20** as a white solid, m.p. 62–63 °C (lit.⁴⁰ 61.5–62.5 °C); ^1H NMR (CDCl_3 , 400 MHz) δ 5.42 (2 H, s, CH_2), 7.34–8.12 (15 H, m, Ph); ^{13}C NMR (CDCl_3 , 100 MHz) 66.6 (CH_2), 127.2, 127.5, 127.6, 128.5, 128.9, 129.8, 130.2, 133.2, 135.1, 140.8, 141.3 (Ph), 166.6 (C=O); HRMS [M + Na]⁺ calcd for $\text{C}_{20}\text{H}_{16}\text{O}_2\text{Na}$ *m/z* 311.1043, found 311.1042.



Characterization data for adduct of benzoate ester of isonitroso dimethylbarbituric acid and 4-phenylbenzyl alcohol, compound (21)

¹H NMR (CDCl₃, 400 MHz) δ 3.01 (3 H, s, Me), 3.05 (3 H, s, Me), 5.29 (1 H, d, *J* 12 Hz, CH₂), 5.41 (1 H, d, *J* 12 Hz, CH₂), 7.42–7.85 (14 H, m, 2 × Ph, C₆H₄); ¹³C NMR (CDCl₃, 100 MHz) δ 25.54, 26.15, 69.32, 82.3, 126.4, 127.2, 127.3, 127.4, 127.6, 127.7, 128.5, 128.8, 128.9, 129.0, 129.4, 129.2, 129.4, 132.8, 134.1, 140.4, 142.2, 155.9, 162.3, 164.8, 166.3; HRMS [M + H]⁺ calcd for C₂₆H₂₃N₃O₆ *m/z* 474.1620, found 474.1659.

Methyl 3-O-benzoyl 4,6-O-benzylidene-β-D-galactopyranoside (23)

A mixture of methyl 4,6-O-benzylidene-β-D-galactopyranoside (22) (0.100 g, 0.354 mmol), benzoylating reagent (1.1 equivalent), and Et₃N (0.060 mL, 0.42 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (75–85% EtOAc/petroleum ether) of the residue afforded the 3-benzoate 23 as a white solid, m.p. 163–164 °C (lit.³⁶ m.p. 166–167 °C); [α]_D +94 (c 1.0, CHCl₃; lit.³⁶ [α]_D +95); ¹H NMR (CDCl₃, 400 MHz) δ 2.34 (1 H, d, *J* 2.4 Hz, OH), 3.60–3.62 (4 H, m, H₅, CH₃), 4.11 (1 H, dd, *J* 12.5, 1.7 Hz, H₆), 4.18 (1 H, ddd, *J* 10.1, 7.8, 2.5 Hz, H₂), 4.41–4.36 (2 H, m, H_{1,6}), 4.51 (1 H, d, *J* 3.6 Hz, H₄), 5.15 (1 H, dd, *J* 10.1, 3.7 Hz, H₃), 5.53 (1 H, s, PhCH), 7.29–8.12 (10 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 57.4 (CH₃), 66.7, 68.9, 69.1, 73.7, 74.3, 100.9, 104.2 (C₁), 126.2, 128.1, 128.5, 128.9, 129.8, 130.0, 133.4, 137.7 (Ph), 166.6 (C=O); HRMS [M + H]⁺ calcd for C₂₁H₂₂O₇Na *m/z* 409.1254, found 409.1254.

Methyl 2-O-benzoyl 4,6-O-benzylidene-α-D-glucopyranoside (25)

A mixture of methyl 4,6-O-benzylidene-α-D-glucopyranoside (24) (0.100 g, 0.354 mmol), 1.4 equivalents of the benzoylating reagent and Et₃N (0.060 mL, 0.415 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (25–35% EtOAc/petroleum ether) of the residue afforded the 2-benzoate 25 as a white solid, m.p. 169–170 °C (169–170 °C); [α]_D +108 (c 1.0, CHCl₃; lit.¹⁶ [α]_D +107); ¹H NMR (CDCl₃, 400 MHz) δ 2.57 (1 H, s, OH), 3.40 (3 H, s, CH₃), 3.63 (1 H, t, *J* 9.4 Hz, H₆), 3.80 (1 H, t, *J* 10.3 Hz, H₆), 3.91 (1 H, ddd, *J* 9.8, 9.8, 4.7 Hz, H₅), 4.34 (2 H, m, H_{3,4}), 5.04 (1 H, dd, *J* 9.5, 3.8 Hz, H₂), 5.08 (1 H, d, *J* 3.8 Hz, H₁), 5.58 (1 H, s, PhCH), 7.36–8.13 (10 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 55.7 (CH₃), 62.2, 69.0, 69.1, 74.2, 81.6, 97.9, 102.2 (C₁), 126.4, 128.5, 128.6, 129.4, 130.1, 133.5, 137.1 (Ph), 166.3 (C=O); HRMS [M + H]⁺ calcd for C₂₁H₂₂O₇Na *m/z* 409.1257, found 409.1260.

Methyl 2,3-di-O-benzyl-6-O-benzoyl-α-D-glucopyranoside (27)

A mixture of benzoyl-Oxyma 13 (0.092 g, 0.374 mmol), methyl 2,3-di-O-benzyl-α-D-glucopyranoside 26⁴¹ (0.100 g, 0.267 mmol) and Et₃N (0.050 mL, 0.32 mmol) in dry CH₂Cl₂ (3.0 mL) at

0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried over (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (30–40% EtOAc/petroleum ether) of the residue afforded 27 (0.11 g, 86%), m.p. 77–79 °C (lit.⁴² 75–77 °C); [α]_D +35 (c 0.25, CHCl₃; lit.⁴² [α]_D +25); ¹H NMR (CDCl₃, 400 MHz) δ 2.53 (1 H, d, *J* 2.9 Hz, OH), 3.40 (3 H, s, CH₃), 3.53 (2 H, m, H_{4,5}), 3.87 (2 H, m, H_{2,3}), 4.51 (1 H, dd, *J* 12.1, 2.1 Hz, H₆), 4.59–4.68 (3 H, m, H_{1,6,CH₂}), 4.77 (2 H, dd, *J* 11.6, 10.3 Hz, CH₂Ph), 5.01 (1 H, d, *J* 11.3, CH₂Ph), 7.28–8.02 (15 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 55.3, 63.8, 69.5, 70.2, 73.3, 75.7, 79.7, 81.3, 98.2 (C₁), 128.0, 128.1, 128.2, 128.4, 128.6, 128.7, 129.8, 133.2, 138.0, 138.7 (Ph), 166.8 (C=O); HRMS [M + Na]⁺ calcd for C₂₈H₃₀O₇Na *m/z* 501.1884, found 501.1886.

4-Methylphenyl 3,4-O-(2',3'-dimethoxybutan-2',3'-diyl)-6-O-benzoyl-1-thio-α-D-mannopyranoside (29)

A mixture of benzoyl-Oxyma 13 (0.036 g, 0.146 mmol), 3,4-di-O-(2,3-dimethoxybutane-2,3-diyl)-α-D-mannopyranoside 28⁴³ (0.042 g, 0.105 mmol), and Et₃N (0.020 mL, 0.126 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried over (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (50–70% EtOAc/petroleum ether) of the residue afforded 29 as a syrup (0.030 g, 50%), [α]_D +167.8 (c 0.25, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 1.30 (3 H, s, CH₃), 1.34 (3 H, s, CH₃), 2.27 (3 H, s, CH₃Ar), 3.17 (3 H, s, OCH₃), 3.32 (3 H, s, OCH₃), 4.07 (1 H, dd, *J* 9.1, 3.0 Hz, H₂), 4.18–4.22 (2 H, m, H_{3,6}), 4.49 (1 H, ddd, *J* 11.9, 6.1 Hz, H₆), 4.55–4.65 (2 H, m, H_{4,5}), 5.52 (1 H, s, H₁), 6.98–8.01 (10 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 14.1 (CH₃), 17.7 (CH₃), 17.8, 21.2, 29.8, 48.1, 48.3, 63.0, 64.1, 64.7, 67.1, 69.7, 72.7, 87.1, 100.2, 100.5, 107.1, 125.8, 128.4, 128.54, 129.2, 129.7, 129.8, 130.0, 130.0, 130.7, 132.7, 133.1, 133.3, 135.3, 138.2, 157.1 (Ph), 160.7, 165.9, 166.4 (C=O); HRMS [M + H]⁺ calcd for C₂₆H₃₂O₈SNa *m/z* 527.1701 found 527.1705.

Methyl 3-O-benzyl-6-O-benzoyl-α-D-glucopyranoside (31)

A mixture of benzoyl-Oxyma 13 (0.121 g, 0.491 mmol), methyl 3-O-benzyl-α-D-glucopyranoside 30⁴⁴ (0.100 g, 0.351 mmol) and Et₃N (0.060 mL, 0.421 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried over (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (40–50% EtOAc/petroleum ether) of the residue afforded 31 as a white solid (0.13 g, 55%), m.p. 70–71 °C; [α]_D +88.0 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 2.27 (1 H, d, *J* 8.3 Hz, OH), 2.83 (1 H, d, *J* 3.2 Hz, OH), 3.45 (3 H, s, CH₃), 3.54 (1 H, ddd, *J* 9.1, 9.1, 2.3 Hz, H₄), 3.63 (1 H, dd, *J* 8.4, 8.4 Hz, H₃), 3.69 (1 H, ddd, *J* 9.1, 3.8 Hz, H₂), 3.87 (1 H, ddd, *J* 9.8, 4.7, 2.2 Hz, H₅), 4.52 (1 H, dd, *J* 12.1, 2.2 Hz, H₆), 4.67 (1 H, dd, *J* 12.1, 4.7 Hz, H₆), 4.77–4.83 (2 H, m, H_{1,CH₂}), 4.98 (1 H, d, *J* 11.4, CH₂), 7.29–8.08 (10 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 55.4 (CH₃), 63.7, 69.9, 69.9, 72.7, 75.3, 82.5, 99.6 (C₁), 120.3, 128.1, 128.5, 128.7, 129.8, 129.8, 133.3, 138.5 (Ph),



167.0 (C=O); HRMS [M + H]⁺ calcd for C₂₁H₂₄O₇ Na *m/z* 411.1414, found 411.1412.

Methyl 3-O-benzyl-2,6-di-O-benzoyl- α -D-glucopyranoside (32)

A mixture of benzoyl-Oxyma **13** (0.194 g, 0.787 mmol), of methyl 3-O-benzyl- α -D-glucopyranoside **30**⁴⁴ (0.080 g, 0.281 mmol) and Et₃N (0.05 mL, 0.337 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried over (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (30–40% EtOAc/petroleum ether) of the residue afforded **32** as a syrup (0.0600 g, 41%), [α]_D +100.4 (*c* 0.5, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 3.42 (3 H, s, CH₃), 3.72 (1 H, t, *J* 9.1 Hz, H4), 3.98 (1 H, ddd, *J* 10.1, 4.4, 2.2 Hz, H5), 4.08 (1 H, t, *J* 9.0 Hz, H3), 4.56 (1 H, dd, *J* 12.1, 2.2 Hz, H6), 4.73–4.79 (2 H, m, H2,6), 4.88 (1 H, d, *J* 11.3 Hz, CH₂Ph), 5.07–5.12 (2 H, m, H1,CH₂Ph), 7.48–8.12 (10 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 55.4 (CH₃), 63.6, 69.7, 70.4, 73.9, 75.5, 79.6, 82.5, 97.5, 99.6 (C1), 128.0, 128.1, 128.5, 128.6, 128.7, 129.7, 129.8, 129.9, 129.9, 130.2, 133.3, 133.4, 133.5, 138.1 (Ph), 160.0, 167.1 (C=O); HRMS [M + H]⁺ calcd for C₂₈H₂₈O₈Na *m/z* 515.1676 found 515.1668.

Phenyl 3,6-di-O-benzoyl- β -D-glucopyranoside (34)

A mixture of benzoyl-Oxyma **13** (0.210 g, 0.853 mmol), phenyl β -D-glucopyranoside **33** (0.100 g, 0.390 mmol) and Et₃N (0.060 mL, 0.468 mmol) in dry CH₂Cl₂ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with CH₂Cl₂, washed with water (2 × 20 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash chromatography (2–5% acetone/CH₂Cl₂) of the residue afforded **34** as a white solid (0.11 g, 55%), m.p. 144 °C; [α]_D +2.7 (*c* 0.5, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 2.81 (1 H, s, OH), 3.49 (1 H, s, OH), 3.83 (1 H, t, *J* 9.3 Hz, H4), 3.90 (1 H, ddd, *J* 9.7, 6.1, 2.3 Hz, H5), 4.00 (1 H, dd, *J* 9.1, 8.0 Hz, H2), 4.63 (1 H, dd, *J* 12.0, 6.1 Hz, H6), 4.74 (1 H, dd, *J* 12.0, 2.3 Hz, H6), 5.07 (1 H, d, *J* 7.7 Hz, H1), 5.33 (1 H, t, *J* 9.1 Hz, H3), 7.07–8.08 (15 H, m, Ph); ¹³C NMR (CDCl₃, 100 MHz) 63.0, 69.7, 72.2, 74.6, 78.6 (C2,3,4,5), 101.0 (C1), 117.0, 123.2, 128.5, 128.6, 129.3, 129.6, 129.7, 129.9, 130.1, 133.4, 133.7, 157.0 (Ph), 166.9, 167.6 (C=O); HRMS [M + H]⁺ calcd for C₂₆H₂₄O₈Na *m/z* 487.1363, found 487.1361.

X-ray crystallography

Crystals of **13** and **14** were mounted in low temperature oil then flash cooled using an Oxford low temperature device. Intensity data were collected at 130 K on an Oxford SuperNova X-ray diffractometer with CCD detector using Cu-Kα (α = 1.54184 Å) radiation. Data were reduced and corrected for absorption. The structures were solved by direct methods and difference Fourier synthesis using the SHELX suite of programs⁴⁵ as implemented within the WINGX software.⁴⁶ Thermal ellipsoid plots were generated using the program ORTEP-3.

Crystal data for **13**: C₁₂H₁₀N₂O₄ *M* = 246.22, *T* = 130.0(1) K, λ = 1.54184, monoclinic, space group *P*2₁/*n*, *a* = 11.8867(1), *b* =

8.0556(1), *c* = 12.3853(1) Å, β = 99.064(1), *V* = 1171.14(2) Å³, *Z* = 4, *D*_c = 1.396 g cm⁻³, μ (Cu-Kα) 0.904 mm⁻¹, *F*(000) = 512, crystal size 0.49 × 0.44 × 0.32 mm. 8000 reflections measured, 2434 independent reflections (*R*_{int} = 0.0170), the final *R* was 0.0342 [*I* > 2σ(*I*) 2347 data] and *wR*(*F*²) (all data) was 0.0966. CCDC deposition: 1406156.

Crystal data for **14**: C₁₄H₁₄N₂O₄ *M* = 274.27, *T* = 130.0(1) K, λ = 1.54184 Å, monoclinic, space group *P*2₁/*n*, *a* = 5.9020(1), *b* = 21.5230(3), *c* = 11.2041(2) Å, β = 102.073(2)°, *V* = 1391.76(4) Å³, *Z* = 4, *D*_c = 1.309 g cm⁻³, μ (Cu-Kα) 0.813 mm⁻¹, *F*(000) = 576, crystal size 0.50 × 0.15 × 0.06 mm. 9619 reflections measured, 2897 independent reflections (*R*_{int} = 0.0299), the final *R* was 0.0392 [*I* > 2σ(*I*) 2605 data] and *wR*(*F*²) (all data) was 0.1018. CCDC deposition: 1406157.

Spectrophotometric titrations

Dissociation constants (pK_a values) of the oximes or HOBT were measured spectrophotometrically using a Cary-50 Bio UV/Vis spectrophotometer in 95% (v/v) MeCN-water at wavelengths of 220–315 nm. Buffer solutions across the pH range of 2–10 were prepared by adding 0.2 M NaOH to a mixture of 0.04 M phosphoric acid, acetic acid, and boric acid. HOBT or oximes at 0.1 mM concentration were prepared in the buffer solutions and the absorbance measured. Each cuvette contained 50 μL of 1 mM stock solution of oxime or HOBT in MeCN, 100 μL of 40 mM buffer, and 1.85 mL of MeCN were used to obtain a final concentration of 0.025 mM of the reagent. Absorbances were measured at the wavelength where the difference between the absorbance of the oxime or HOBT, and its conjugate base was maximized. Titration curves are provided in the ESI.†

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