JOC*Note*

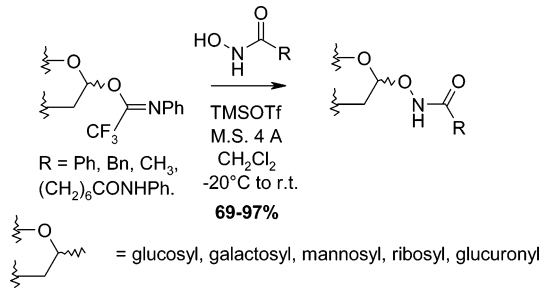
First *O*-Glycosylation of Hydroxamic Acids

Mickaël Thomas, Jean-Pierre Gesson, and Sébastien Papot*

UMR 6514, Synthèse et Réactivité des Substances Naturelles, Université de Poitiers et CNRS, 40, Av. du Recteur Pineau, 86022 Poitiers, France

sebastien.papot@univ-poitiers.fr

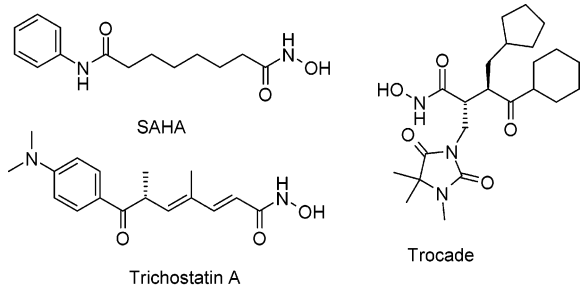
Received January 30, 2007



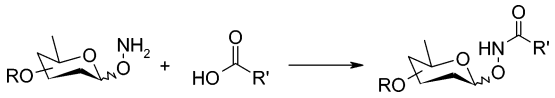
The first *O*-glycosylation of hydroxamic acids is reported. This process involves the use of glycosyl *N*-phenyl trifluoroacetimidates as glycosyl donors in the presence TMSOTf and 4 Å molecular sieves in dichloromethane. Under such conditions, a wide range of new glycosyl donors including glucosyl, galactosyl, mannosyl, glucuronyl, and ribosyl hydroxamates were prepared in good to high yields. This procedure appears to be an advantageous alternative for the synthesis of glycosyl hydroxamates of biological interest.

Over the past decade, hydroxamic acid-containing derivatives have emerged as a class of compounds of great therapeutical interest especially with respect to inhibition of histone deacetylases[1] (HDACs) and matrix metalloproteases (MMPs).[2] Some of them, such as SAHA[3] and Trocade,[4] are currently undergoing clinical trials for the indications of cancer and rheumatoid arthritis, respectively (Scheme 1). More recently, the *O*-glycosyl hydroxamate counterparts appeared as compounds of biological relevance too. For example, Trichostatin D, the α-glucosyl derivative of the potent HDAC inhibitor Trichostatin A (TSA), is an inducer of phenotypic reversion in oncogene-transformed cells and as a consequence is expected to be a selective antitumor agent.[5] The glucuronylated derivatives of SAHA and Trocade are major metabolites of the corresponding drug substances.[6,7] In a recent study, the *β*-*O*-galactoside of SAHA has been reported as a promising prodrug for selective cancer chemotherapy.[8]

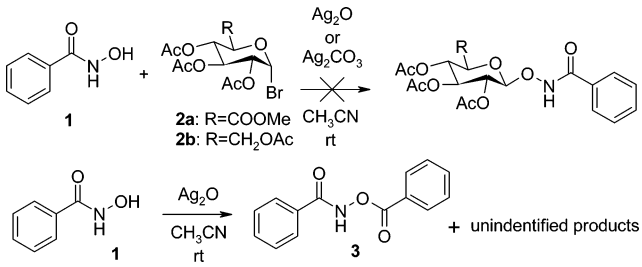
SCHEME 1. Some Hydroxamic Acid-Containing Drugs



SCHEME 2. Preparation of Glycosyl Hydroxamates by Amidation of Carboxylic Acids with *O*-gLycosyl Hydroxylamines



SCHEME 3. Glycosylation Attempts of Hydroxamic Acid 1 under Koenigs−Knorr Conditions



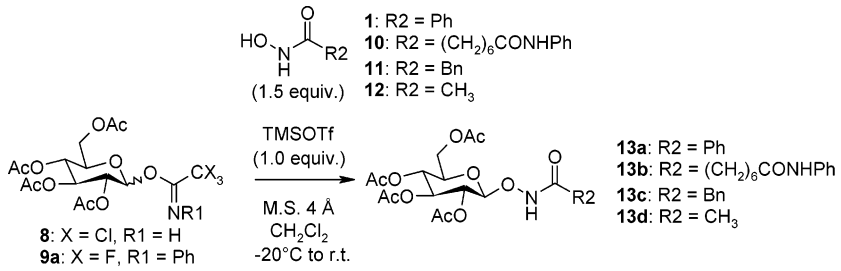
Surprisingly, despite the rising interest in *O*-glycosyl hydroxamates, no direct method for the glycosylation of hydroxamic acids has been reported in the literature. To date, the sole known methodology for preparing such carbohydrate derivatives involves amidation of the corresponding carboxylic acids with *O*-glycosyl hydroxylamines (Scheme 2).[7−9] Therefore, the development of an effective glycosylation method of hydroxamic acids is particularly warranted. This paper reports our investigations in this area that led with success to the first stereoselective and high-yielding *O*-glycosylation of hydroxamic acids.

Our initial efforts focused upon the coupling of commercially available benzhydroxamic acid **1** to the well-known methyl 2,3,4-tri-O-acetyl-α-D-glucopyranosyluronate bromide **2a**[10] in the presence of either Ag_2O or Ag_2CO_3 (Scheme 3). In spite of several attempts, using various amounts of glycosyl donor **2a** (ranging from 1 to 2.5 equiv), coupling between **1** and **2a** always failed and resulted in a complex mixture presumably due to the instability of the hydroxamic acid toward silver salts. This

(1) For a review see: Monneret, C. *Eur. J. Med. Chem.* **2005**, *40*, 1−13.
(2) For a review see: Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735−2776.
(3) Krug, L. M.; Curley, T.; Schwartz, L.; Richardson, S.; Marks, P.; Chiao, J.; Kelly, W. K. *Clin. Lung Cancer* **2006**, *7*, 257.
(4) Hemmings, F. J.; Farhan, M.; Roland, J.; Banken, L.; Jain, R. *Rheumatology* (*Oxford*) **2001**, *40*, 537−543.
(5) Hayakawa, Y.; Nakai, M.; Furihata, K.; Shin-ya, K.; Seto, H. *J. Antibiot.* **2000**, *53*, 179−183.
(6) Du, L.; Musson, D. G.; Wang, A. Q *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, March 13−17, 2005; ; American Chemical Society: Washington, DC, 2005.
(7) Mitchell, M. B.; Whitcombe, I. W. A. *Tetrahedron Lett.* **2000**, *41*, 8829−8834.
(8) Thomas, M.; Rivault, F.; Tranoy-Opalinski, I.; Roche, J.; Gesson, J.-P.; Papot, S. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 983−986.
(9) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333−337.
(10) Bollenback, G. N.; Long, J.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310−3315.

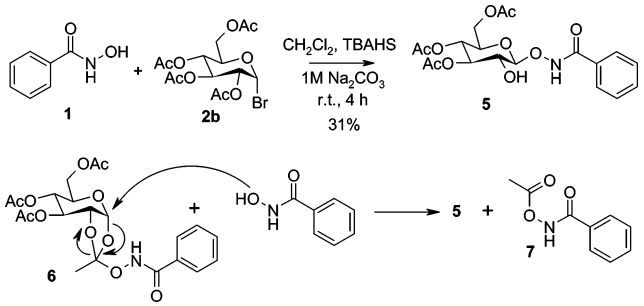
10.1021/jo0701839 CCC: $37.00
Published on Web 04/28/2007

TABLE 1. ***O*-Glycosylation of Hydroxamic Acids with Glucosyl Imidates 8 and 9**



entry	donor	acceptor	product **13**	yield (%)	α:β
1	**8**	**1**	**13a**	80	β only
2	**8**	**10**	**13b**	54	β only
3	**8**	**11**	**13c**	60	β only
4	**8**	**12**	**13d**	45	β only
5	**9**	**1**	**13a**	97	β only
6	**9**	**10**	**13b**	90	β only
7	**9**	**11**	**13c**	97	β only
8	**9**	**12**	**13d**	97	β only

SCHEME 4. Glycosylation of Hydroxamic Acid 1 under Phase Transfer Catalyzed Conditions



hypothesis was supported by TLC analysis that indicated total consumption of **1** under all tested Koenigs−Knorr conditions whereas **2a** appeared to be mostly unreactive. Thus, to confirm such a hypothesis, hydroxamic acid **1** was dissolved in CH_3CN in the presence of Ag_2O. In this case, rapid degradation of **1** was observed leading mainly to the formation of *N*,*O*-diacylhydroxylamine **3**[11] together with several unidentified products. On the other hand, no degradation was detected without silver salts. Thus, since further attempts with the more reactive[12] bromoglucoside **2b** afforded similar results, we considered it preferable to employ glycosylation methods avoiding the use of silver salts as activating reagents.

We next investigated glycosylation of benzhydroxamic acid **1** under phase transfer catalysis (PTC) conditions. This method has been used successfully with a wide number of nucleophiles employing bromo sugars as glycosyl donors.[13] Glycosylation was performed with glucosyl bromide **2b** and 5 equiv of **1** with methylene chloride as the organic phase and 1 M Na_2CO_3 as the aqueous phase in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) as catalyst (Scheme 4). After 4 h at room temperature, acetobromoglucose **2b** was totally consumed leading to the 2-*O*-deacetylated glucosyl hydroxamate **5** with complete β-selectivity though only in moderate yield (31%). Initially, the β-stereoselectivity of this glycosylation reaction appeared surprising taking into account the absence of any participating group at C-2 in the final product **5**. However, a careful analysis of the reaction mixture allowed the isolation of the *O*-acetylated hydroxamic acid **7**, which provided us an interesting clue for explaining the formation of **5**. Thus, it may be postulated that the synthesis of the later proceeded via the nucleophilic attack of benzhydroxamic acid **1** by the β-face of the previously formed orthoester **6** followed by subsequent elimination of **7** (Scheme 4).

Further attempts with lower amounts of **1** were undertaken under the PTC conditions described above. However, since all these experiments afforded **5** in lower yields, we decided to turn our attention to other procedures such as imidate-mediated glycosylations.

Glycosyl trichloroacetimidates, introduced by Schmidt and co-worker in 1980,[14] are among the most widely used glycosyl donors.[15] Such derivatives are easily accessible from the corresponding 1-hydroxy sugars by treatment with trichloroacetonitrile in the presence of a suitable base and require mild activation conditions, using in most cases TMSOTf or $BF_3.Et_2O$ as promoters.

Thus, to examine coupling reactions between these glycosyl donors and hydroxamic acids, we first prepared α-glucosyl trichloroacetimidate **8** from β-D-glucose pentaacetate in two steps according to literature procedures.[16] Various substituted commercially available hydroxamic acids **1**, **11**, and **12** as well as the HDAC inhibitor SAHA **10** were chosen for this study. As depicted in Table 1, glycosylation reactions were conducted with 1.5 equiv of each hydroxamic acid in the presence of an equimolar amount of TMSOTf and 4 Å MS at −20 °C in dichloromethane. In all cases, glycosylations provided the corresponding *O*-glucosyl hydroxamates **13** exclusively as the

(11) Schraml, J.; Sykora, J.; Fiedler, P.; Roithova, J.; Mindl, J.; Blechta, V.; Cisarova, I.; Exner, O. *Org. Biomol. Chem.* **2004**, *2*, 2311−2314.

(12) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763−4766.

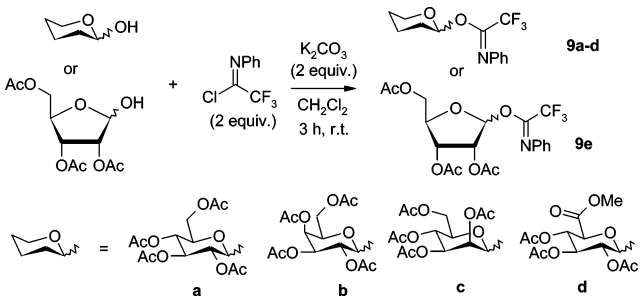
(13) For a review see: Roy, R. In *Phase transfer catalysis in carbohydrate chemistry*; Sasson, Y., Neumann, R., Eds.; Handbook of Phase Transfer Catalysis; Chapman and Hall: Glascow, UK, 1997; Chapter 7, pp 244−272.

(14) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *19*, 731−732.

(15) For a review see: Schmidt, R. R.; Jung, K.-H. In *Preparative carbohydrate chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(16) Cook, B. N.; Bhakta, S.; Biegel, T.; Bowman, K. G.; Armstrong, J. I.; Hemmerich, S.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 8612−8622.

TABLE 2. Synthesis of Glycosyl *N*-Phenyl Trifluoroacetimidates 9a−e



entry	sugar	product **9**	yield (%)
1	D-glucose	**9a**	99
2	D-galactose	**9b**	93
3	D-mannose	**9c**	80
4	D-glucuronic acid	**9d**	95
5	D-ribose	**9e**	87

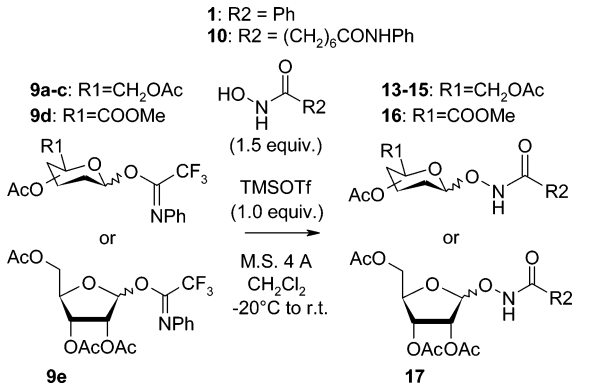
β-anomers in good yields after purification by flash column chromatography (entries 1−4).

At this stage, we considered it worthwhile to pursue our investigations in this direction by studying other imidate types as glycosyl donors. Within this framework, glycosyl trifluoroacetimidates[17] have been recently introduced as valuable alternatives to their trichloroacetimidate analogues and used advantageously in sialylation[18] and glycosylation of amides.[19] Therefore, to examine the glycosylation of hydroxamic acids with such donors we first synthesized the novel glucosyl *N*-phenyl trifluoroacetimidate **9a** in quantitative yield from 2,3,4,6-tetra-*O*-acetyl-D-glucose and *N*-phenyl trifluoroacetimidoyl chloride[20] employing the procedure described by Yu et al. (Table 2).[17] As illustrated in Table 1, use of donor **9a** afforded β-glucosyl hydroxamates **13** in dramatically increased yields (>90%, entries 5−8) compared to those obtained with trichloroacetimidate **8** (45−80%, entries 1−4).

In light of these results, we next investigated *O*-glycosylation of hydroxamic acids **1** and **10** with a range of glycosyl imidates **9** previously prepared in nearly quantitative yields following the procedure mentioned above (Table 2).[17] It is worth noting that most glycosyl trifluoroacetimidates **9** were not stable for long periods and consequently were used rapidly after flash column chromatography purification.

As shown in Table 3, all glycosylation reactions gave good to excellent yields (69−97%) of the expected coupling products, including the two glycosylated SAHA derivatives **14b** and **16b** recently introduced as compounds of biological relevance (entries 4 and 8, 69% and 78%, respectively).[6,8] It should be mentioned that this new glycosylation method brings a real improvement for the preparation of such SAHA derivatives with regard to yields, number of steps, and the accompanying decrease in loss of material, compared to the synthesis recently reported in the literature.[8]

TABLE 3. *O*-Glycosylation of Hydroxamic Acids with Glucosyl Imidates 9a−e



entry	sugar	donor **9**	acceptor	product	yield (%)	α:β
1	D-glucose	**9a**	**1**	**13a**	97	β only
2	D-glucose	**9a**	**10**	**13b**	90	β only
3	D-galactose	**9b**	**1**	**14a**	80	β only
4	D-galactose	**9b**	**10**	**14b**	69	β only
5	D-mannose	**9c**	**1**	**15a**	92	α only
6	D-mannose	**9c**	**10**	**15b**	84	α only
7	D-glucuronic acid	**9d**	**1**	**16a**	80	β only
8	D-glucuronic acid	**9d**	**10**	**16b**	78	β only
9	D-ribose	**9e**	**1**	**17a**	81	β only
10	D-ribose	**9e**	**10**	**17b**	69	β only

In conclusion, we have demonstrated the first efficient *O*-glycosylation of hydroxamic acids with glycosyl *N*-phenyl trifluoroacetimidates as sugar donors and TMSOTf as promoter in dichloromethane. This method appears to be general and appropriate to the preparation of a wide range of glycosyl hydroxamates. Additionally, since this glycosylation reaction has been applied with success to the synthesis of glycosyl derivatives of SAHA, this finding may open a new door for the investigation of biological properties of this family of carbohydrate derivatives. Indeed, we believe this glycosylation method should be very useful for the preparation of glycosyl of hydroxamic acid-containing drugs.

Experimental Section

General Procedure for the *O*-Glycosylation of Hydroxamic Acids. A mixture of glycosyl donor **9** (1.0 equiv), hydroxamic acid (1.5 equiv), and freshly activated 4 Å molecular sieves (4 g/mmol) in anhydrous dichloromethane (10 mL/mmol) was stirred at room temperature for 1 h under N_2 to remove traces of water, and then cooled to −20 °C. TMSOTf (1.0 equiv) was added. The mixture was then allowed to warm to room temperature. After being stirred for 3 h, the reaction mixture was quenched by the addition of Et_3N (1 mL/mmol). The resulting mixture was filtered through Celite and $MgSO_4$. The filtrate was concentrated under reduced pressure and then subjected to flash column chromatography.

Acknowledgment. The authors thank CNRS, La Ligue Nationale contre le Cancer, and the Région Poitou-Charentes for financial support of this study.

Supporting Information Available: General experimental information, spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) and copies of ^{1}H NMR and ^{13}C NMR spectra for all new glycosyl trifluoroacetimidate donors **9** and new glycosyl hydroxamates **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0701839

(17) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405−2407. (b) Yu, B.; Tao, H. J. *J. Org. Chem.* **2002**, *67*, 9099−9102.
(18) Cai, S.; Yu, B. *Org. Lett.* **2003**, *5*, 3827−3830.
(19) Tanaka, H.; Iwata, Y.; Takahashi, D.; Adachi, M.; Takahashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 1630−1631.
(20) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−35.