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Concise Approach to Novel Isothiazolidinone Phosphotyrosine Mimetics: Microwave-Assisted Addition of Bisulfite to Activated Olefins

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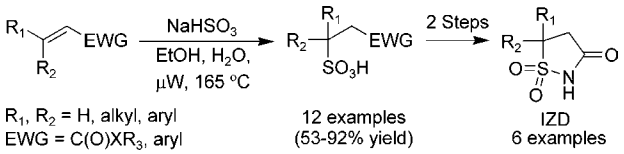
ABSTRACT

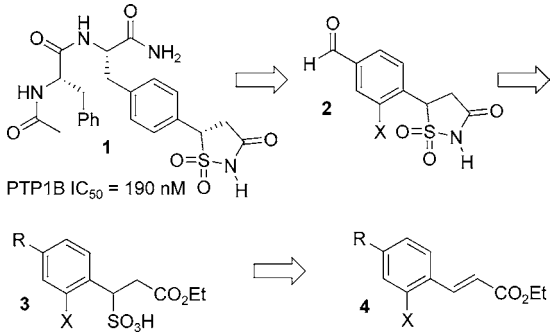


A novel and efficient synthesis of isothiazolidinone protein tyrosine phosphatase mimetics is presented. A practical, regiospecific microwave-assisted addition of bisulfite to activated olefins, including unprecedented reactions with styrene derivatives, is highlighted.

The rising incidence of type 2 diabetes and obesity has accelerated the search to find effective agents to treat these diseases. Protein tyrosine phosphatase 1B (PTP1B) is highly validated as a target for drug discovery. PTP1B knockout studies have shown lowered blood glucose levels and improved insulin responsiveness.[1] Thus, the design and synthesis of inhibitors of PTP1B has been a focus of the pharmaceutical industry and academic research.[2]

Recently, we reported a structure-based design of potent PTP1B inhibitor **1** (Scheme 1)[3] that incorporated the novel 1,1-dioxidoisothiazolidin-3-one (IZD) protein tyrosine-phosphatase (pTyr) mimetic via a Suzuki coupling to a phenylalanine boronic acid scaffold with a 5-chloroisothiazolone. While this approach allowed for efficient synthesis of PTP1b inhibitor **1**, several important targets **2** with selected ortho substituents (X) were not accessible utilizing this chemistry. A novel route to the IZD **2** was envisioned utilizing a bisulfite addition to readily available enoate **4** to form sulfonic acid **3**, followed by cyclization (see Scheme 1). Reaction of bisulfite with α,β-unsaturated ketones, esters, and amides has been known for over a century.[4] However, there are few

Scheme 1. Retrosynthetic Analysis of PTP1B Inhibitors



(1) (a) Elchebly, M.; Payette, P.; Michaliszyn, E.; Cromlisch, W.; Collins, S.; Loy, A. L.; Normandin, D.; Cheng, A.; Himms-Hagen, J.; Chan, C.; Ramachandran, C.; Gresser, M. J.; Tremblay, M. L.; Kennedy, B. P. *Science* **1999**, *283*, 1544.

(2) For recent comprehensive reviews, see: (a) Bialy, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3814. (b) Ross, S. A.; Gulve, E. A.; Wang, M. *Chem. Rev.* **2004**, *104*, 1255. (c) Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nature Rev.* **2002**, *1*, 696.

(3) Combs, A. P.; Yue, E, Bower, M.; Ala, P. J.; Wayland, B.; Douty, B.; Takvorian, A.; Polam, P.; Wasserman, Z.; Zhu, W.; Crawley, M. L.; Pruitt, J.; Sparks, R.; Glass, B.; Modi, D.; McLaughlin, E.; Bostrom, L.; Li, M.; Galya, L.; Blom, K.; Hillman, M.; Gonnville, L.; Reid, B.; Wei, M.; Becker-Pasha, M.; Klabe, R.; Huber, R.; Li, Y.; Hollis, G.; Burn, T. C.; Wynn, R.; Liu, P.; Metcalf, B. *J. Med. Chem.* **2005**, in press.

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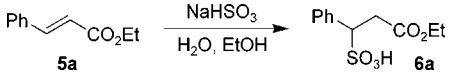
reported uses of it. Most examples are on highly activated disubstituted enones or require long reaction times.[5]

We report herein a practical and general approach for regiospecific addition of sodium bisulfite to activated olefins. The sulfonic acid adducts' utility is demonstrated by the rapid assembly of the recently reported IZD class of pTyr mimetics.

Ethyl cinnamate **5a** was used as a model system to optimize sodium bisulfite addition conditions that would allow for exploration of a variety of substituted olefin derivatives (Table 1). A solvent mixture of ethanol and water was selected to promote solubility of both the organic reactant and the bisulfite salt. While reaction with sodium bisulfite did proceed slowly at vigorous reflux (Table 1, entries 1 and 2), clean conversion to product **6a** was obtained in a matter of minutes in the microwave at 165 and 180 °C (Table 1, entries 4 and 5). While microwave tubes are designed to withstand pressure up to 21 bar, we recommend maintaining pressure under 15 bar.

Table 1. Optimization of Sodium Bisulfite Addition Conditions



entry	heating[b]	T (°C)	pressure (bar)	time (min)	conv[c] (%)
1	oil bath	125	1	30	5
2	oil bath	125	1	180	32
3	oil bath	165	*d*	30	56
4	**microwave**	**165**	**12**	**30**	**>95**
5	microwave	180	17	10	>95

[a] Conditions: 1.0 equiv of ethyl cinnamate, 2.0 equiv of sodium bisulfite, 1:1 = H_2O/EtOH, 1.0 M concentration. [b] Heating at 165 and 180 °C was done in 1.0 mL total solvent volume (1.0 mmol scale) in 10 mL sealed μW tubes. [c] Determined by LCMS with monitoring UV at 220 nM. [d] Pressure was not determined.

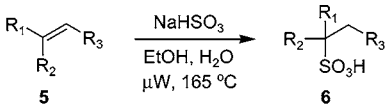
Utilizing these optimized microwave-assisted conditions a variety of β-aryl enoates were investigated as substrates for sodium bisulfite additions (Table 2).

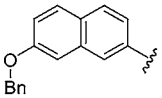
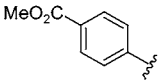
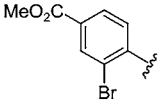
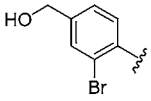
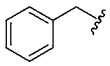
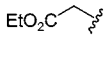
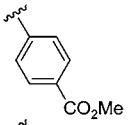
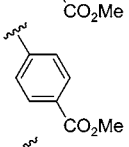
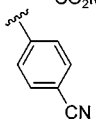
The expected products (**6a**−**e**) were initially isolated by preparative HPLC/LCMS chromatography. However, on a gram scale it was more convenient to isolate sulfonic acid adducts via crystallization, which afforded comparable yields.

To explore the scope of the reaction, less reactive and more hindered substrates were investigated. While in some cases these examples required longer reaction times, cinnamide **5f**, ethyl 3,3-dimethylacrylate **5g**, and cyclic enoate **5h** (Table 2) afforded moderate to high yields of adducts **6f**−**h** utilizing the optimized reaction conditions. In the case of enoate **5g**, the higher temperature and pressure in the microwave were critical as the reaction did not proceed even after 24 h at reflux in an oil bath.

Additional compounds with a methylene spacer between the aryl ring and the IZD, substituted 4-but-2-enoic acid ethyl esters, were examined as substrates. The first derivative **5i** afforded a high yield (87%) of product **6i**. In attempts to prepare further alkyl enoate derivatives, substituted styrene **5j** was prepared with conjugation to the aryl ring instead of

Table 2. Synthesis of Sulfonic Acids **6** via Microwave-Assisted Additions of Sodium Bisulfite to Activated Olefins **5**

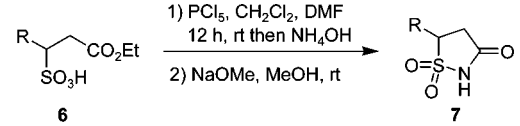


5 / **6**	R_1	R_2	R_3	time (h)	yield (%)
5a / **6a**		H	CO_2Et	0.5	92
5b / **6b**		H	CO_2Et	0.5	92
5c / **6c**		H	CO_2Et	0.5	86
5d / **6d**		H	CO_2Et	0.5	85
5e / **6e**		H	CO_2Me	0.5	77
5f / **6f**		H	$C(O)NH_2$	1.0	53
5g / **6g**	Me	Me	CO_2Et	1.0	91
5h / **6h**	OH			0.5	84
5i / **6i**		H	CO_2Et	0.5	87
5j / **6j**		H		1.0	83
5k / **6k**	H	H		1.5	62
5l / **6l**	H	H		1.5	71

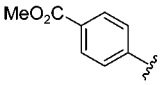
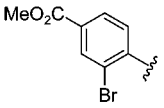
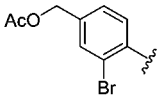
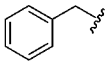
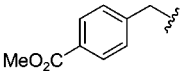
(4) For early representative examples,, see: (a) Beilstein, F. K.; Wiegand, H. *Chem. Ber.* **1885**, *18*, 482. (b) Dodge, F. D. *J. Am. Chem. Soc.* **1930**, *52*, 1724. (c) Thurston, J. T. U.S. Patent 2,402,512, 1944.

(5) For more recent representative examples, see: (a) Kellogg, R. M.; Nieuwenhuijzen, J. W.; Pouwer, K.; Vries, T. R.; Broxterman, Q. B.; Grimbergen, R. F. P.; Kaptein, B.; La Crois, R. M.; de Wever, E.; Zwaagstra, K.; van der Laan, A. C. *Synthesis* **2003**, *10*, 1626. (b) Baczko, K.; Chasseray, X.; Larpent, C. *J. Chem. Soc., Perkin Trans. 2* **2001**, *2*, 2179. (c) Hejchman, E.; Haugwitz, R. D.; Cushman, M. *J. Med. Chem.* **1995**, *38*, 3407. (d) Pfoertner, K. H. *Helv. Chim. Acta* **1980**, *63*, 664.

Table 3. Synthesis of Novel Isothiazolidinone **7**



6 **7**

6 / **7**	R	yield (%)[a]
6a / **7a**		52
6c / **7c**		50
6d / **7d**		58
6m[b] / **7e**		56
6i / **7i**		54
6j / **7j**		79

[a] Isolated yields for two steps. [b] The hydroxyl group of **6e** was acyl protected to form **6m** before attempting the amination/cyclization.

the ester.[6] Unexpectedly, this derivative **5j** afforded desired adduct **6j** under the optimized conditions. The result can be rationalized by the high temperature and pressure isomerizing the olefin into conjugation with the ester, allowing for the desired Michael-type addition of bisulfite. However, it is plausible that regiospecific addition to styrene **5j** was in fact the underlying process.

To test the hypothesis that activated styrenes could be substrates for bisulfite addition, two electron-deficient monosubstituted derivatives (**5k** and **5l**) were prepared and subjected to the reaction conditions (Table 2). While the reactions required additional time relative to the enoate examples, clean conversions to **6k** and **6l** were achieved with moderate isolated yields (62% and 71%, respectively). This constitutes the first examples of sodium bisulfite adding to monosubstituted derivatives to afford β-aryl sulfonic acids as the major products.[7]

To obtain the desired IZDs **7**, the appropriate sulfonic acids **6** were converted to sulfonamides via the acid chlorides and subsequently cyclized (see Table 3).[8] The conditions for both steps afforded a minimal amount of elimation product (enoates **5**). In the case of sulfonic acid **6d**, acyl protection (**6m**) of the free alcohol was required before amination and cyclization.

In summary, we have developed an efficient route to access a novel class of phosphotyrosine (pTyr) mimetics employing a practical and general microwave-assisted bisulfite addition to activated olefins. The bisulfite chemistry developed herein utilizes readily accessible olefins with a variety of substitution and is highly amenable to parallel synthesis. Of note, the styrene derivatives **5j**−**l**, were identified as relatively unactivated substrates for this microwave-assisted process. The utilization of this new methodology to synthesize novel PTP1B inhibitors containing IZD pTyr mimetics will be reported elsewhere.[9]

Supporting Information Available: General experimentals and analytical data for **6a**−**l** and **7a**,**c**,**d**,**i**,**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The initially desired adduct in this preparation was the enoate.

(7) There is a report of the reaction of styrene with sodium bisulfite to give this type of adduct as the major product by: (a) Kharasch, M. S.; May, E. M.; Mayo, F. R. *J. Org. Chem.* **1938**, *3*, 175. However, this was later described by the authors in a subsequent publication identifying the major product as 2-hydroxy-2-phenylethanesulfonic acid: (b) Kharasch, M. S.; Schenck, R. T. E.; Mayo, F. R. *J. Am. Chem. Soc.* **1939**, *61*, 3092.

(8) Chen, Z.; Demuth, T. P.; Wireko, F. C. *Biorg. Med. Chem. Lett.* **2001**, *11*, 2111.

(9) Combs, A. P.; Yue, E. W.; Bower, M. J.; Zhu, W.; Crawley, M. L.; Sparks, R. B.; Pruitt, J.; Takvorian, A. Int. Patent WO 2005/035551 A2, 2005.