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One-Pot *o*-Nitrobenzenesulfonylhydrazide (NBSH) Formation−Diimide Alkene Reduction Protocol

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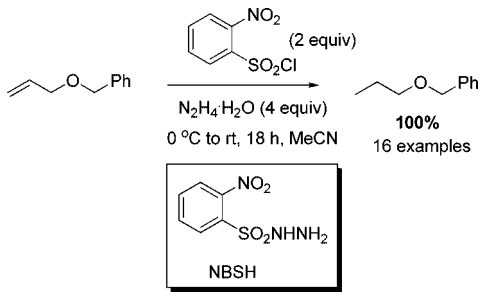
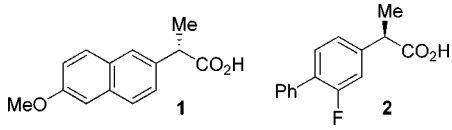


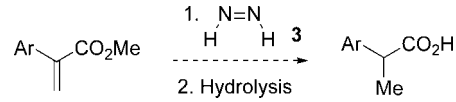
A one-pot protocol for the formation of 2-nitrobenzenesulfonylhydrazide (NBSH) from commercial reagents and subsequent alkene reduction is presented. The transformation is operationally simple and generally efficient for effecting diimide alkene reductions. A range of 16 substrates have been reduced, highlighting the unique chemoselectivity of diimide as a reduction system.

Aryl propionic acids constitute an important class of nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Important examples of 2-aryl propionic class of NSAID are naproxen **1** and flurbiprofen **2**.[2]



These compounds find continued use in the treatment of pain, fever, and a range of inflammations. Furthermore, with Alzheimer's disease a growing concern for an aging global population, several studies suggest NSAIDs such as **2** offer potential as preventative medicines against Alzheimer's disease.[3] Therefore, flexible and rapid routes to 2-aryl propionic acids will continue to be of interest to the organic synthesis and medicinal chemistry communities.

SCHEME 1



As part of a collaborative program to study novel 2-aryl propionic acids, we required a versatile and rapid route to racemic structures. The reduction of 2-aryl methyl acrylates[4] was chosen as our synthetic route because a diverse range of substrates are readily accessible.[5] However, a non-transition-metal-catalyzed hydrogenation protocol was essential as functionality present in many of the required structures would be sensitive to hydrogenation conditions. For example, structures possessing sensitive alkenes, benzylic ethers, and benzylic amines were required. Accordingly, the possibility of examining *cis*-diimide **3** (diazene) as a chemoselective reductant for our context was considered (Scheme 1).[6]

The use of diimide as a reduction strategy can offer a number of synthetic advantages. High substrate *chemo-* and *regio*selectivity, compatibility with sensitive functionality,[7] and close control of reductant stoichiometry are all possible in diimide alkene reductions. Furthermore, the use of diimide can be advantageous with respect to transition-metal-catalyzed hydrogenations as alkene isomerization and epimerization can be avoided using diimide.[8] Diimide is known to efficiently reduce symmetrical, nonpolarized alkenes and has been suggested to be ineffective with polarized alkenes.[6] However, Buszek has recently demonstrated that a cinnamate ester underwent efficient reduction[9] by diimide generated from 2-nitrobenzenesulfonylhydrazide (NBSH, **5a**).[10−12] Furthermore, a number of cinnamates have been reduced by diimide formed from sulfonylhydrazides other than NBSH.[13] This reagent, popularized by Myers for the synthesis of allenes from propargyl alcohols[14] and reductive transposition of allylic alcohols,[15] offers itself as a particularly mild *cis*-diimide precursor for alkene reduction.[16] To explore this strategy, the NBSH-mediated reduction of 2-phenyl methyl acrylate (**4**) to form 2-phenyl methyl propionate (**6**) was examined (Table 1).

(1) Lombardino, J. G. *Nonsteroidal Anti-inflammatory Drugs*; Wiley Interscience, John Wiley & Sons: New York, 1983.

(2) For a review of 2-aryl propionic acids and their synthesis, see: Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(3) For discussions concerning the preventative treatment of Alzheimer's disease using NSAIDs, see: (a) Weggen, S.; Rogers, M.; Eriksen, J. *Trends Pharmacol. Sci.* **2007**, *28*, 536. (b) Vlad, S. C.; Miller, D. R.; Kowall, N. W.; Felson, D. T. *Neurology* **2008**, *70*, 1672.

(4) For examples of 2-aryl acrylate ester hydrogenation, see: Dumont, W.; Poulin, J. C.; Dang Tuan, P.; Kagan, H. B. *J. Am. Chem. Soc.* **1973**, *95*, 8295.

(5) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584.

(6) For a review of diimide as a hydrogenation reagent, see: Pasto, D. J.; Taylor, R. T. In *Organic Reactions*; John Wiley & Sons: Hoboken, NJ, 1991; Vol. 40, p 91.

(7) Cloarec, J.-M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 4731.

(8) For a discussion of the potential synthetic issues of heterogenous hydrogenation, see: Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482.

(9) Buszek, K. R.; Brown, N. *J. Org. Chem.* **2007**, *72*, 3125.

(10) For the first use of NBSH in diimide-mediated alkene hydrogenations, see: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771.

(11) Dann, A. T.; Davies, W. *J. Chem. Soc.* **1929**, 1050.

(12) For a flavin-catalyzed generation of diimide, see: Imada, Y. Iida, H. Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544. See also ref 8.

(13) Lacombe, P.; Castagner, B.; Gareau, Y.; Ruel, R. *Tetrahedron Lett.* **1998**, *39*, 6785.

(14) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(15) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

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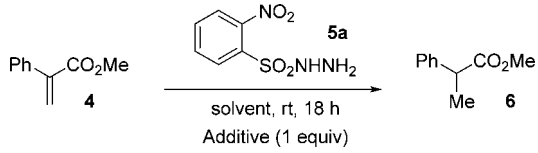
TABLE 1. Optimization of Diimide Reduction of 2-Phenyl Methyl Acrylate (4) Mediated by NBSH



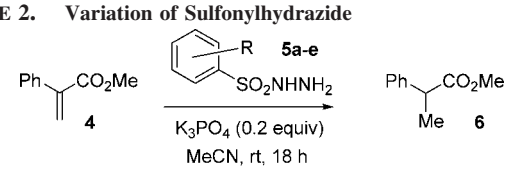
entry	equiv of **5a**	solvent	additive	conversion (%)[a]
1	2	MeCN		11
2	3	MeCN		38
3	3	DCM		6
4	3	Tol		5
5	3	Et_2O		0
6	3	THF		36
7	3	MeCN	Et_3N	35
8	2	MeCN	LiOAc	25
9	2	MeCN	$NaHCO_3$	17
10	2	MeCN	$NaCO_3$	76
11	2	MeCN	NaOH	100
12	2	MeCN	KCl	11
13	2	MeCN	$KHCO_3$	100
14	2	MeCN	KOAc	100
15	2	MeCN	K_3PO_4	99
16	2	MeCN	K_3PO_4[b]	94
17	2	MeCN	K_3PO_4[c]	47
18	1.5	MeCN	K_3PO_4[b]	75

[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] 0.2 equiv added. [c] 0.1 equiv added.

Initial examinations demonstrated that acrylate **4** was indeed fairly unreactive. Mixing 2 equiv of NBSH **5a** and acrylate **4** in acetonitrile at room temperature led to reduction with 11% conversion after 18 h (entry 1). Repeating with a further equivalent of **5a** (entry 2) led to an increased conversion of 38%. Acetonitrile was observed to be the best solvent: THF was of comparable efficiency, but dichloromethane, toluene, and diethyl ether were observed to be ineffective solvents (entries 3−6). Reductions mediated with **5a** are often conducted in the presence of a basic additive such as triethylamine.[9,16a-c,e-g] However, in this context, the presence of triethylamine made little difference to the reduction of **4** (entry 7). Interesting results were observed when a range of inorganic bases were examined. Notably, a number of inorganic additives allowed for a full conversion of **4**. Accordingly, the addition of 1 equiv of NaOH, $KHCO_3$, KOAc, or K_3PO_4 to the reaction mixture improved conversion dramatically (entries 11, 13, 14, and 15). From the data presented, two trends appear. First, the inorganic cation is important, with potassium seen to be most favorable (cf. entries 8, 14 and 9, 13). Second, the pK_a of the anion is also important as seen by the sodium salts (entries 9−11) and the potassium salts used (entries 12−15). Furthermore, it should be noted that substoichiometric amounts (20%) of potassium phosphate can be used without affecting this reduction reaction (entry 16).

The effect of the sulfonylhydrazide diimide source upon this reduction reaction was next investigated. Four additional sulfonylhydrazides (**5b**−**e**) were compared with NBSH **5a**, allowing for variation in the steric and electronic nature of the sulfonylhydrazide to be studied (Table 2).

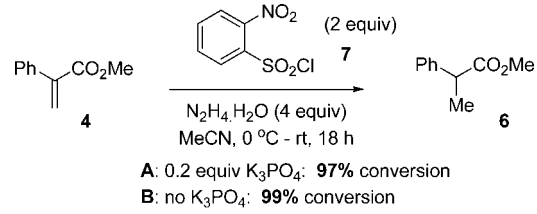
TABLE 2. Variation of Sulfonylhydrazide



entry	R	equiv of **5**	conversion (%)[a]
1	2-NO_2 **5a**	2	94
2	2,4,6-^{i}Pr **5b**	2	33
3	2-CF_3 **5c**	2	28
4	3-NO_2 **5d**	2	0
5	4-NO_2 **5e**	2	0

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.

SCHEME 2



Reduction was only observed using sulfonylhydrazides **5b** and **5c**, but with markedly less efficiency compared to 2-NBSH **5a** (Table 2, entries 1−3). The use of 3-NBSH **5d** and 4-NBSH **5e** failed to hydrogenate acrylate **4** (Table 2, entries 4 and 5). These results suggest that the formation of diimide from sulfonylhydrazide precursors is strongly dependent on both electronic and steric influences, with ortho-substitution essential.

With optimum conditions at hand, we chose to study a range of alkene substrates to determine whether this practical protocol was general. However, to ensure reproducibility, two subsequent attempts to reduce **4** disappointingly showed only ca. 50% conversion. This poor reproducibility was later ascribed to a deterioration of **5a** on storage.[17] While this observation was disappointing and testified to the thermal and moisture sensitivity of **5a**, it left us to ponder the feasibility of forming NBSH in situ, in the presence of the alkene. Such a protocol would have obvious advantages over the need to pre-prepare and store **5a**. Therefore, an adaptation of Myers' procedure for the preparation of **5a**[18] was attempted through the slow addition of 4 equiv of hydrazine monohydrate to a solution of **4**, potassium phosphate, and 2 equiv of 2-nitrobenzenesulfonyl chloride **6** at 0 °C before warming to room temperature (Scheme 2).

Gratifyingly, ^{1}H NMR analysis showed complete consumption of **4** after 18 h. Of particular interest is the observation that, when forming **5a** in situ, the presence of K_3PO_4 is now not essential for excellent conversion, in contrast to the earlier protocol using preformed **5a** (conditions B), presumably due to excess hydrazine hydrate fulfilling a similar role to the inorganic additive.

A range of alkenes were, in turn, screened using this improved one-pot protocol to determine the scope of this novel reduction protocol (Figure 1). Each substrate was submitted to standard

(16) For recent examples of NBSH-mediated alkene and alkyne hydrogenation, see: (a) Fuwa, H.; Goto, T.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2211. (b) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 2283. (c) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109. (d) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5015. (e) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703. (f) Jung, W.-H.; Harrison, C.; Shin, Y.; Fournier, J.-H.; Balachandran, R.; Raccor, B. S.; Sikorski, R. P.; Vogt, A.; Curran, D. P.; Day, B. W. *J. Med. Chem.* **2007**, *50*, 2951. (g) Guppi, S. R.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 4966. (h) von Seebach, M.; Kozhushkov, S. I.; Schill, H.; Frank, D.; Boese, R.; Benet-Buchholz, J.; Yufit, D. S.; de Meijere, A. *Chem.—Eur. J.* **2007**, *13*, 167.

(17) ^{1}H NMR and melting point analysis suggested the decomposition of NBSH in our hands. It has been reported that **5a** is stable for 2 months at −20 °C; see ref 14.

(18) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

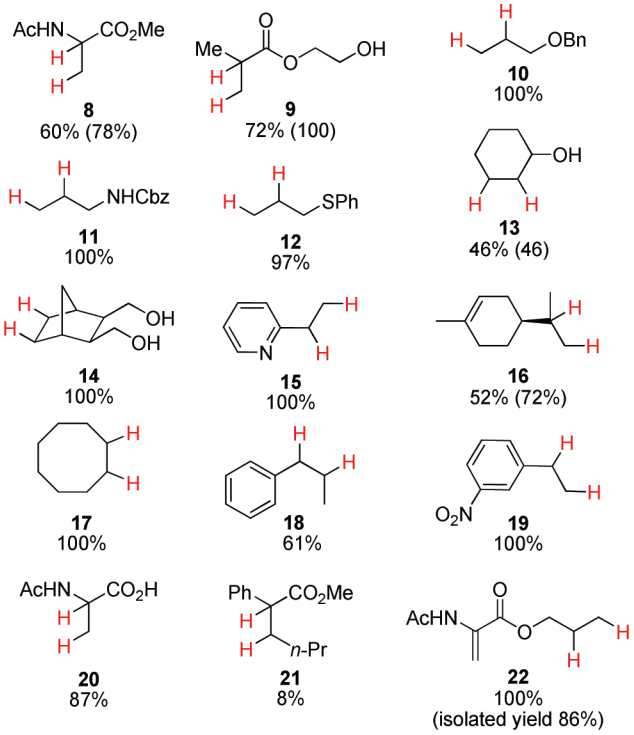


FIGURE 1. Comparative study: scope of alkene substrate using one-pot protocol. Transferred hydrogens shown in red. Conditions: 2-$NO_2C_6H_4SO_2Cl$ (2 equiv), $NH_2NH_2 \cdot H_2O$ (4 equiv), MeCN (0.2 M), 0 °C to rt, 18 h. Conversions in parentheses conducted over 42 h.

conditions (conditions B, Scheme 2) and therefore Figure 1 provides a handle on the relative reactivity of diimide with various alkenes.

This reduction protocol is effective and highly regio- and chemoselective for the reduction of terminal alkenes and alkenes with relatively low levels of substitution. The chemoselectivity is highlighted in the case of **10**, **11**, and **19**, which possess functional groups which would be readily reduced through the use of heterogeneous hydrogenation protocols. Alkene substrates which contain Lewis basic sites which may disrupt standard heterogeneous hydrogenation protocols are not problematic for diimide as seen by the formation of **12** and **15**. The high levels of regioselection observed when using *cis*-diimide are highlighted through the formation of **16** and **22** with the less substituted alkene and electronically neutral alkene reduced preferentially in each example. Additionally, it can be clearly seen that diimide does in fact readily react with polarized alkenes such as acrylates and acrylic acids, forming **6**, **8**, **9**, and **20** in good yield. Only when the level of substitution increases does the reaction become less efficient, as seen by the low conversion on forming **21**. In cases where full conversion is not observed, an improved conversion can often be obtained through an extended reaction time.

In conclusion, a one-pot 2-nitrobenzenesulfonylhydrazide forming−alkene reduction protocol has been developed. This transformation proceeds through the generation of the reductant *cis*-diimide via the one-pot formation of NBSH (**5a**). This protocol has been used to demonstrate the chemo- and regioselectivity of alkenes in diimide reductions. We believe the protocol is particularly practical and may offer an advantageous alternative to transition-metal-catalyzed hydrogenation of alkenes in a number of synthetic situations.

Experimental Section

General Procedure of One-Pot NBSH Formation−Alkene Reduction. To a cooled (0 °C) and vigorously stirred solution of 2-nitrobenzenesulfonylchloride (442 mg, 2 mmol) and alkene (1 mmol) in dry MeCN (5 mL) was added hydrazine hydrate (194 μL, 4 mmol) slowly via the side of the reaction flask over a period of 1 min. The resulting white suspension was allowed to slowly warm to room temperature, stirring vigorously for a further 18 h. After this time, H_2O (5 mL) was added and the crude product extracted with pentane (4 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and filtered prior to removal of solvent in vacuo to provide the desired crude product with further purification by column chromatography, if necessary, on silica gel.

Propyl 2-Acetamidoacrylate 22. Following the general procedure using 2-nitrobenzenesulfonylchloride (442 mg, 2 mmol), allyl 2-acetamidoacyrlate (169 mg, 1 mmol), and hydrazine hydrate (194 μL, 4 mmol) in MeCN (5 mL), **22** was isolated after column chromatography purification, eluting with EtOAc/petroleum ether (4:1) at 40−60 °C as a clear oil (147 mg, 0.86 mmol, 86%): ν_{max} (film)/cm^{-1} 2970, 2881, 1719, 1674, 1634, 1509; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.96 (3H, t, J = 7.7 Hz), 1.71 (2H, qt, J = 7.7, 6.7 Hz), 2.10 (3H, s), 4.17 (2H, t, J = 6.7 Hz), 5.85 (1H, d, J = 1.4 Hz), 6.55 (1H, s), 7.74 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 10.5, 22.1, 24.9, 67.9, 108.3, 131.3, 164.4, 168.9; HRMS (ESI) m/z calcd for $C_8H_{13}NO_3Na$ $[M + Na]^+$ 194.0793, found 194.0781.

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Supporting Information Available: Experimental details, ^{1}H and ^{13}C spectra of a novel compounds, and ^{1}H NMR spectra of crude reaction mixtures depicting reaction conversions are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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