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Chemoselective Hydrogenation Reaction of Unsaturated Bonds in the Presence of an *o*-Nitrobenzenesulfonyl Group

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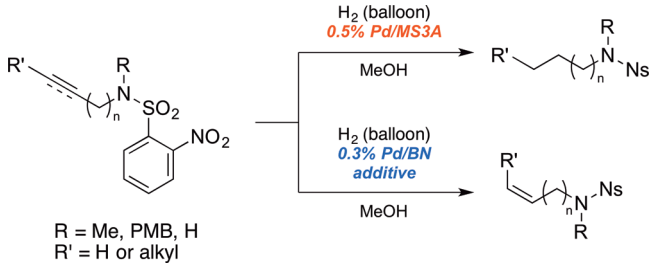
ABSTRACT



Chemoselective hydrogenation of unsaturated compounds bearing an *o*-nitrobenzenesulfonyl (Ns)-amide moiety, affording the corresponding saturated compounds, was accomplished efficiently without loss of the nitro group by using the Pd/MS3A catalyst and a H_2 balloon. Partial hydrogenation of alkynes bearing an Ns group to corresponding *cis* alkenes was achieved with the combination of the Pd/BN catalyst and an additive (diethylenetriamine or acetic acid).

The development of synthetic methods for the obtention of nitrogen-containing compounds has attracted much attention, mainly because these compounds often possess a variety of interesting biological activities. We have developed an efficient synthetic methodology for primary and secondary amine synthesis by employing nitrobenzenesulfonamides (Ns-amides).[1] This strategy enables selective preparation of secondary amine synthesis from primary amines, as shown in Scheme 1.[2] In addition, the reactions of Ns-NH_2 and its derivatives, such as *N*-Boc-Ns-NH and *N*-Cbz-Ns-NH, can produce protected primary amines from the corresponding alcohols *via* the Mitsunobu reaction (Method A) or from alkyl halides *via* conventional alkylation reactions (Method B).[3]

Furthermore, the high alkylation ability of Ns-amides permits the efficient construction of macrocyclic amines without the need for high dilution conditions.[1−4] Although this strategy has great potential, there is a serious limitation: commonly used heterogeneous Pd-catalyzed hydrogenation conditions cannot be applied, because the nitro group on the sulfonylbenzene ring, which is essential for removal of the Ns group *via* a Meisenheimer complex,[1,2] is considered to be highly sensitive to such conditions (see Table 1, entries 1−5). During our synthetic studies on natural products, we needed to achieve selective partial hydrogenation of an alkyne in the presence of an Ns group. Therefore, we set out to develop a suitable reaction for this purpose, anticipating that such a selective reduction

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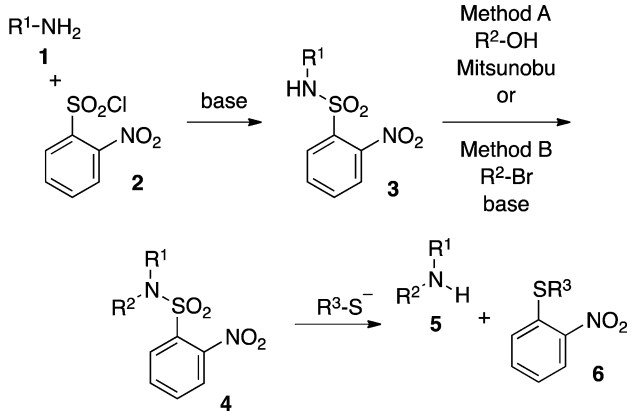
Scheme 1. Conversion of Primary Amines to Secondary Amines *via* the Ns Strategy

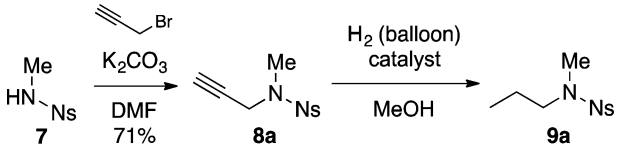


reaction would further enhance the synthetic utility of our Ns-strategy.

Recently, one of the authors (H.S.) has developed heterogeneous Pd-catalysts,[5] such as Pd/MS3A[5h,j] and Pd/BN (Pd/boron nitride),[5i] which are useful for chemoselective hydrogenation of unsaturated bonds without decomposition of various reducible functional groups including *N*-Cbz, *O*-benzyl, nitro, and azide groups. Therefore, we speculated that such Pd catalysts would be suitable for the desired selective hydrogenation of unsaturated compounds bearing an Ns group, even though the nitro group is activated by the neighboring sulfonylamide group. Herein, we report the chemoselective hydrogenation of unsaturated bonds linked to an Ns-amide moiety by using a Pd/MS3A or Pd/BN catalyst system.

To establish appropriate reaction conditions, we examined the hydrogenation of *N*-methyl-*N*-propargyl Ns-amide (**8a**), which was readily prepared by the alkylation reaction of *N*-methyl Ns-amide (**7**)[3] with propargyl bromide (Table 1). While reactions with 5% Pd/C, Lindlar's catalyst[6] [Pd/$CaCO_3$ poisoned with $Pb(OAc)_2$], PtO_2, 5% Rh/C, and Wilkinson's catalyst [$RhCl(PPh_3)_3$][7] gave an inseparable mixture resulting from the undesired reduction

Table 1. Catalytic Activity for the Selective Hydrogenation



entry	catalyst (wt %)	time (h)	yield[a] (%)
1	5% Pd/C (10)	1	–[b]
2	5% Lindlar (10)	3	–[c]
3	5% PtO_2/C (10)	1	–[c]
4	5% Rh/C (10)	1	–[c]
5	Wilkinson's cat. (10)	1	–[d]
6	0.5% Pd/MS3A (15)	22	80
7	0.5% Pd/MS3A (25)	12	85
8	0.5% Pd/MS3A (50)	2	86

[a] Isolated yield. [b] An inseparable mixture of alkane and reduced aniline derivative was formed.[8] [c] A reduced aniline derivative was formed.[8] [d] An inseparable mixture of alkane and alkene was formed.[8]

of the nitro group (entries 1–5),[8] we found that the reaction of Ns-amide **8a** with H_2 (delivered from a balloon) and Pd/MS3A (15 wt %) in MeOH for 22 h proceeded smoothly to give the corresponding saturated alkane **9a** in 80% yield (entry 3). In this reaction, no appreciable reduction of the nitro group was observed. Increasing the amount of Pd/MS3A from 15 to 25 wt % resulted in faster conversion, affording **9a** in 85% yield after 12 h (entry 4). With 50 wt % of the Pd/MS3A catalyst, the reaction was completed in only 2 h, and **9a** was obtained in 86% yield.

With optimized conditions in hand, we examined the generality of this reaction using several alkyne or alkene substrates bearing Ns-amide. As shown in Table 2, chemoselective conversions to the corresponding alkanes were accomplished without any loss of the nitro group in the Ns-amide. This method was applicable to a variety of terminal alkynes **8a**–**8f** (entries 1–6) as well as internal alkynes **8g**–**8l** (entries 7–12), with excellent yields. Furthermore, internal alkenes **8m**–**8o** (entries 13–15) were also reduced cleanly to the corresponding alkanes **9d**–**9f** with 0.5% Pd/MS3A (100 wt %) over 10–15 h in excellent yields. In these reactions, an acidic Ns-amide proton did not inhibit the reaction (entries 3, 6, 9, and 12).

Notably, removal of the PMB protecting group was not observed (entries 2, 5, 8, 11, and 14).[9]

Next, we turned our attention to selective partial hydrogenation of alkynes bearing Ns-amide to the corresponding *cis*-alkenes. While Lindlar's catalyst[6] has been the catalyst of choice for this transformation, the reaction of nitrobenzene compounds containing alkynes is difficult to perform without reduction of the nitro group (see also

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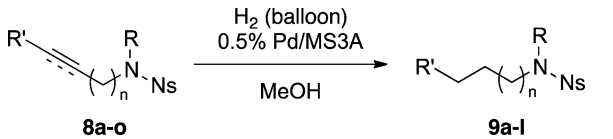
(8) Hydrogenation reactions of **8a** with these catalysts in other solvents (*n*-hexane, THF, EtOAc) were also investigated. For details, see Supporting Information.

(9) Hydrogenation reactions of *N*-Boc-*N*-propargyl Ns-amide and *N*-Cbz-*N*-propargyl Ns-amide were also investigated. However, these reactions failed to give the desired alkanes. Thus, hydrogenation of *N*-Boc-*N*-propargyl Ns-amide did not occur and the starting material was recovered. In the case of *N*-Cbz-*N*-propargyl Ns-amide, the Cbz group was removed without hydrogenation of the alkyne.

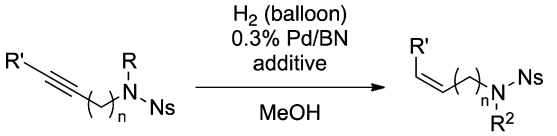
Table 2. Scope of Terminal or Internal Unsaturated Ns-Amides



entry	substrate	R	product	time (h)	yield [a] (%)
1 [b]		Me (**8a**)	**9a**	2	86
2 [b,d]		PMB (**8b**)	**9b**	4	96
3 [b]		H (**8c**)	**9c**	2	94
4 [b]		Me (**8d**)	**9d**	4	91
5 [b]		PMB (**8e**)	**9e**	5	94
6 [b]		H (**8f**)	**9f**	10	99
7 [c]		Me (**8g**)	**9g**	10	85
8 [c]		PMB (**8h**)	**9h**	12	95
9 [c]		H (**8i**)	**9i**	12	86
10 [c]		Me (**8j**)	**9j**	12	82
11 [c]		PMB (**8k**)	**9k**	15	95
12 [c]		H (**8l**)	**9l**	10	83
13 [c]		Me (**8m**)	**9d**	3	82
14 [c]		PMB (**8n**)	**9e**	3	97
15 [c]		H (**8o**)	**9f**	20	78

[a] Isolated yield. [b] The reaction was carried out using 50 wt % of 0.5% Pd/MS3A. [c] The reaction was carried out using 100 wt % of 0.5% Pd/MS3A. [d] MeOH/THF = 10/1 was used.

Table 3. Partial Reduction of Terminal Alkynes Bearing Ns-Amide



entry	substrate	R	product	time (h)	yield [a] (%)
1 [b]		Me (**8a**)	**10a**	2.5	98
2 [b,c]		PMB (**8b**)	**10b**	0.25	88
3 [b]		H (**8c**)	**10c**	4	94
4 [b]		Me (**8d**)	**10d**	1.5	99
5 [b]		PMB (**8e**)	**10e**	1	92
6 [b]		H (**8f**)	**10f**	4	91
7 [c]		Me (**8g**)	**10g**	10	85
8 [c]		PMB (**8h**)	**10h**	10	93
9 [c]		H (**8i**)	**10i**	11	90
10 [d]		Me (**8j**)	**10j**	0.2	97
11 [d]		PMB (**8k**)	**10k**	4	97
12 [d]		H (**8l**)	**10l**	4	95

[a] Isolated yield. [b] The reaction was carried out using 25 wt % of 0.3% Pd/BN and 1.0 equiv of DETA. [c] The reaction was carried out using 20 wt % of 0.3% Pd/BN and 5.0 equiv of AcOH. [d] The reaction was carried out using 100 wt % of 0.3% Pd/BN and 5.0 equiv of AcOH. [e] The reaction was carried out using 50 wt % of 0.3% Pd/BN and 5.0 equiv of AcOH in EtOH/THF = 10/1.

Table 1, entry 2).[10] However, our previous study indicated that the target transformation would be possible with the Pd/BN-diethylenetriamine (DETA) system.[5i] As shown in Table 3, the same alkynes used in Table 2 were tested using Pd/BN-DETA as a catalyst. As we had hoped, selective reduction of terminal alkynes **8a**–**8f** proceeded smoothly, leaving the nitro group intact, affording **10a**–**10f** in excellent yield. However, reaction of the internal alkynes **8g**–**8l** was accompanied by concomitant reduction of the nitro group under the same reaction conditions.[11] To overcome this problem, we examined the effect of additives. After numerous attempts, selective partial hydrogenation of internal alkynes was finally achieved by changing the additive from DETA to acetic acid (AcOH). As shown in entries 7–9, selective reduction of methyl-substituted alkynes **8g**–**8i** was accomplished by using 20 wt % of 0.3% Pd/BN and 5.0 equiv of AcOH, and the desired *cis*-alkenes were obtained in high yields. Even in the case of bulkier *n*-propyl-substituted alkynes **8j**–**8l**, the partial reduction proceeded smoothly to provide the corresponding alkenes **10j**–**10l** in excellent yields, albeit with 100 wt % of catalyst.[12] Since the undesired Pd/BN-catalyzed reduction of nitro groups is assumed to be a result of the Lewis acidic affinity of Pd metal on Pd/BN for the nitro group, this result can be rationalized by assuming that addition of AcOH as a mild acid reduces the affinity, thereby effectively suppressing the reduction of the nitro group.

Finally, we investigated recycling of the Pd-catalyst. The catalyst was easily recovered by simple filtration and rinsing with MeOH. As shown in Table 4, Pd/MS3A could be reused at least three times, generating **9c** with similar chemical yields (85–94%), although the reaction time tended to become longer as the number of runs was increased.

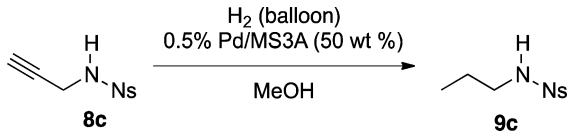
In conclusion, we have demonstrated the chemoselective hydrogenation of unsaturated bonds with Pd/MS3A in compounds bearing an Ns group, which is sensitive to reducing conditions. Moreover, partial hydrogenation of

(10) Hydrogenation reactions of **8a** with Lindlar's catalyst in other solvents (*n*-hexane, THF, EtOAc) were also investigated. However, these reactions failed to give **10a**. For details, see Supporting Information.

(11) In this case, selective partial reduction occurred to afford *cis* olefin and the saturated product was not formed. However, separation from aniline derivatives formed by the undesired reduction of the nitro group was difficult.

(12) Interestingly, Pd/BN-AcOH was not applicable to terminal alkynes **8a**–**8f**. The reaction of these substrates gave the corresponding alkanes **9a**–**9f**. Although the reason for this is not clear, we speculate that AcOH is a weaker catalyst poison than DETA for more sterically less accessible terminal alkynes.

Table 4. Recycling of the Pd/MS3A Catalyst



run	time (h)	yield (%)[a]
1	2	94
2	3	89
3	8	85

[a] Isolated yield.

alkynes bearing Ns-amide to the corresponding *cis*-alkenes was also achieved by using either Pd/BN-DETA or Pd/BN-AcOH without loss of the nitro group. To our knowledge, this is the first example of selective hydrogenation of unsaturated bonds while leaving an Ns group intact. Considering the utility of the Ns-strategy as well as alkene-containing compounds, as exemplified by the olefin metathesis reaction[13] and Mizoroki–Heck reaction,[14] the reaction we report here should be a powerful tool for the synthesis of nitrogen-containing compounds. Further applications of the present methodology are under intensive investigation in our laboratory.

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Supporting Information Available. Experimental procedures and analytical data of new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.