



Reevaluation of the 2-nitrobenzyl protecting group for nitrogen containing compounds: an application of flow photochemistry



Chloe I. Wendell, Michael J. Boyd*

Vertex Pharmaceuticals Inc., 50 Northern Avenue, Boston, MA, United States

ARTICLE INFO

Article history:

Received 5 November 2014

Revised 18 December 2014

Accepted 2 January 2015

Available online 10 January 2015

Keywords:

Photochemistry

Flow

Protecting group

o-Nitrobenzyl

ABSTRACT

Photochemistry under continuous flow conditions has many potential benefits for photochemical reactions that are problematic in batch. The 2-nitrobenzyl moiety is a photolabile protecting group for nitrogen. However, N-deprotection is generally impractical and, therefore, has not been extensively adopted. This Letter reports significant improvements in the N-deprotection of the 2-nitrobenzyl group through the application of continuous flow photolysis. This procedure was applied to a variety of substrates including indoles, indazoles, pyrazoles and secondary amines. Significant improvement in yield, reaction time and scalability was observed under continuous flow conditions.

© 2015 Elsevier Ltd. All rights reserved.

Introduction

The 2-nitrobenzyl protecting group (*o*-NB) is photolabile and removable under mild conditions (Fig. 1). Despite the fact that there are many options for nitrogen protection,¹ the use of ultraviolet light as the sole deprotecting agent makes this protecting group especially useful because the removal conditions are unlikely to affect other functional groups or other protecting groups present in a given substrate. Furthermore, the *o*-NB is stable to a variety of conditions, including acid and base, so it is potentially of high value to synthetic chemists. Its use was first reported by Barltrop in 1966 as the corresponding ester of benzoic acid,² and it was subsequently used for the protection of nitrogen containing compounds such as amines, amides, histidine³ and various heterocycles.⁴

However, apart from amides, the use of the *o*-NB protecting group on nitrogen is relatively uncommon. Potential reasons for the relatively low use of this group for the protection of nitrogen are: (1) removal is often low yielding; (2) long reaction times are often required; (3) very low concentrations are used and (4) reactions are generally limited to a small scale. Scale limitations are due to the decrease of the surface area to reaction volume ratio in conventional batch vessels that leads to decreased light exposure.

Many of the drawbacks seen in *o*-NB removal make the reaction particularly suited to continuous flow photochemical conditions.⁵ In 2005, Booker-Milburn and co-workers⁶ described a practical flow apparatus for organic photochemistry in which the reaction

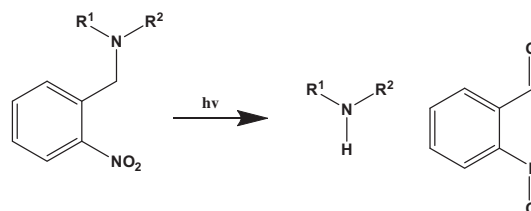


Figure 1. Scheme for the removal of the 2-nitrobenzyl protecting group.

mixture is pumped through UV transparent tubing wrapped around a medium pressure mercury lamp. Compared to batch reactions, photochemical reactions in continuous flow experience more efficient irradiation due to a much higher surface area to volume ratio⁴ and, importantly, this ratio is constant regardless of scale. In addition, more efficient irradiation reduces the duration of the reaction, which can minimize decomposition and side reactions.

To test whether the photolytic deprotection of *o*-NB-protected nitrogen-containing compounds offers significant advantages in flow, several indoles were deprotected in batch and flow and the results were compared. The conditions were then applied to other nitrogen containing compounds.

Batch and flow yields were obtained using the following procedures. In batch reactions, the *o*-NB-protected compounds were added to a 10 mL Pyrex tube under nitrogen. Degassed dioxane (0.04 M) was added and the tube was placed into a Luzchem LZC-4 photoreactor equipped with fourteen 8 W UV-A lamps. In flow, the protected compounds were added to a round bottom flask

* Corresponding author. Tel.: +1 781 961 7440.

E-mail address: Michael_Boyd@vrtx.com (M.J. Boyd).

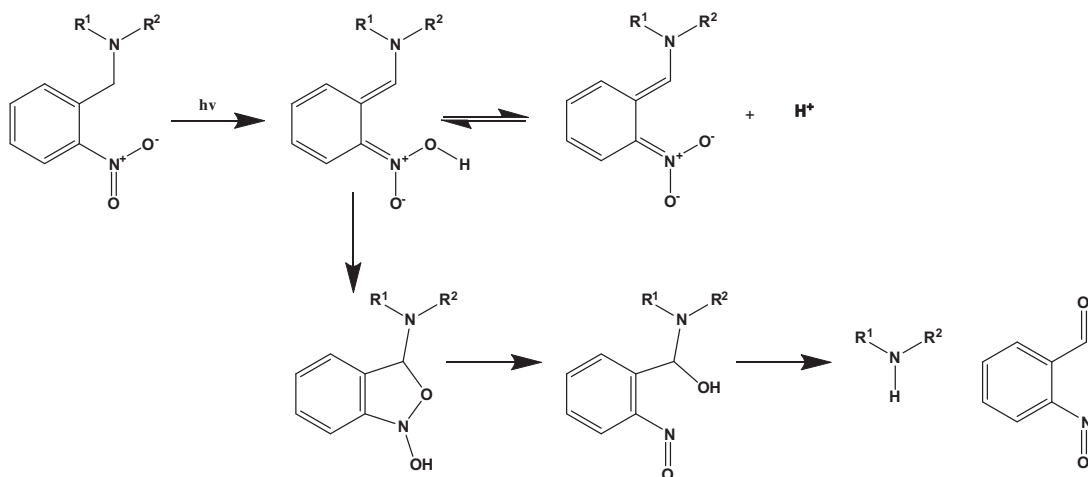


Figure 2. Mechanism of removal of the 2-nitrobenzyl protecting group.

Table 1
Deprotection of indoles in batch and in flow reaction conditions^a

Entry	Substrate	Scale (mg)	Yield in batch (time)	Yield in flow ^b (time)
1		100	40% (18 h)	84% (10 min)
2		100	67% (14 h)	80% (10 min)
3		500	58% (20 h)	
4		100	ND	70% (10 min)
5		100	ND	<30% (20 min)

^a All reaction run at 0.04 M in degassed dioxane.

^b Reactions run at 1 mL/min.

under a nitrogen atmosphere. Degassed dioxane (0.04 M) was then added and the reaction mixture was loaded into a Vapourtec UV 150 flow apparatus equipped with a 10 mL reactor. Flow rates of 0.5–1 mL/min were used. Radiation was filtered with the Gold filter attachment and the lamp was set at an intensity of 70% (effectively 105 W). Both the batch and flow reaction conditions involved exposure of the substrates to a similar range of UV radiation (in the UV-A range).

Results

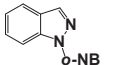
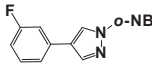
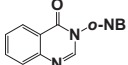
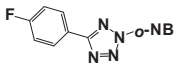
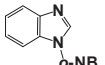
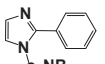
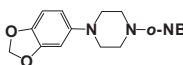
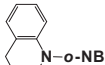
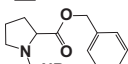
There is only one report of an *o*-NB deprotection of indoles.⁴ The yield reported for deprotection of indole itself was modest (45%). In our hands, under batch conditions, deprotection of indole was incomplete after 24 h and analytically pure indole could not be isolated from the reaction mixture. Therefore, with considerable room for improvement, a *N1-o*-NB-protected indole represented an appropriate first substrate to evaluate under continuous flow photolytic deprotection conditions.

We started with the relatively electron neutral *o*-NB-protected 6-(pyridin-3-yl)-1*H*-indole. Unlike the deprotection of amines, deprotection of indoles led to formation of a stable hemiacetal

intermediate (Fig. 2).⁴ This intermediate can be rapidly broken down by dissolving the crude reaction in MeOH and adding a few drops of aqueous 6 N NaOH. In our hands, this indole deprotection under batch conditions was low yielding (40%) and required 18 h to complete (Table 1, entry 1). Also, low concentrations were required for the reaction to run to completion, making this procedure very impractical. Under continuous flow conditions, we observed a dramatic increase in yield to 84% for the same substrate. The reaction was also complete in 10 min after a single pass through the system. It was subsequently found that deprotection of an electron poor indole gave better yields in batch mode (67%, entry 2). However, the yield dropped significantly as the scale was increased to 500 mg (entry 3) and in both cases reaction times were long (>14 h). Under continuous flow conditions, the yield increased to 80% and this reaction was also complete after a single 10 min pass through the system.

The deprotection of another electron poor indole was also examined. Under flow conditions, it was found deprotection of *o*-NB protected 5-fluoroindole could be rapidly achieved with a yield of 70% (entry 4). The deprotection of electron rich 5-methoxyindole was inefficient with this procedure. Two passes through the system were required for complete reaction and the yield was poor

Table 2
Deprotection of nitrogen-containing compounds in continuous flow photolysis reaction conditions^a

Entry	Substrate	Yield (time per 100 mg)
1		93% (10 min)
2		88% (10 min)
3		65% (20 min)
4		>10% (10 min)
5		39% (10 min)
6		>10% (10 min)
7 ^b		80% (20 min)
8 ^b		88% (20 min)
9 ^b		79% (10 min)

^a All reaction run at 0.04 M in degassed dioxane with 100–500 mg of starting material.

^b With 5 equiv hydrazine (35% in water).

(<30%, entry 5). Based on these results, and consistent with previous observations,⁴ this procedure appears to be best suited to electron neutral and electron poor indoles.

We then expanded our study to evaluate the photochemical deprotection of other nitrogen containing compounds in continuous flow. It was found that indazole and a pyrazole (Table 2, entries 1 and 2) were rapidly and efficiently deprotected with our procedure with yields >85%. Interestingly, in these cases the formation of hemiacetal intermediate was not observed. To our knowledge, the use of the 2-nitrobenzyl group for the protection of indazoles and pyrazoles has not been reported. The deprotection of quinazolinone was also examined (Table 2, entry 3). This deprotection was relatively slow and two passes were required for complete consumption of the starting material. However, we were still able to isolate the product in 65% yield. The efficiency of this deprotection could potentially be improved by reducing the flow rate or increasing the power output of the UV lamp.

Unfortunately, our procedure was less effective for the deprotection of *o*-NB-protected tetrazole, imidazole and benzimidazole derivatives (Table 2, entries 4–6). In all cases reactions were incomplete. Attempts to increase conversion by reducing flow rate were unsuccessful.

Two previously reported examples of the use of the *o*-NB protecting group with secondary amines were found. In one case a

91% deprotection yield was reported, but the reaction was run on very small scale (4.5 μmol) and at very high dilution (0.0005 M).⁷ The other example involves the deprotection of an amino acid which was also performed on small scale at high dilution (0.35 mmol at 0.003 M) with a yield of 51%.⁸ The encouraging results of continuous flow photolysis of *o*-NB-protected heterocycles prompted us to examine the deprotection of protected secondary amines at much more synthetically practical dilution (0.04 M). Our first attempt involved the deprotection of the piperazine shown in Table 2 entry 7. This reaction resulted mostly in the recovery of unreacted starting material. We hypothesized that the formation of a reactive intermediate related to the expected 2-nitrosobenzaldehyde could be interfering with the reaction. Therefore, we investigated the addition of hydrazine to the reaction to quench any interfering reactive intermediates. When the reaction was performed with 5 equiv of hydrazine, the reaction was complete after a single 10 min pass through the flow system. With this procedure, good yields were obtained for three secondary amines (Table 2, entries 7–9), including an amino acid, with excellent efficiency (600 mg/hr). The high deprotection efficiency observed in these cases suggests that the suitability of the *o*-NB group for the protection of secondary amines may be significantly increased with the use of continuous flow and hydrazine. Interestingly, the addition of hydrazine to the deprotection of nitrogen containing heterocycles resulted in inhibition of the reaction.

Conclusion

With the use of continuous flow photolysis, the 2-nitrobenzyl group can be a practical option for protection of indoles, indazoles, pyrazoles and secondary amines. Improvements in reaction yield, duration and scalability are seen under continuous flow conditions relative to conventional batch reactions.

Acknowledgments

The authors would like to thank John Cochran, Jeremy Green and Mike Arnost for technical assistance and helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.01.007>.

References and notes

- Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339–2358.
- Bartrop, J. A.; Plant, P. J.; Schofield, P. J. *Chem. Commun.* **1966**, 822–823.
- Kalbag, S. M.; Roeske, R. W. *J. Am. Chem. Soc.* **1975**, *97*(2), 440–441.
- Voelker, T.; Ewell, T.; Joo, J.; Edstrom, E. D. *Tetrahedron Lett.* **1998**, *39*, 359–362.
- Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.
- Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558–7564.
- McCulloch, M.; Coombs, G. S.; Banerjee, N.; Bugni, T. S.; Cannon, K. M.; Harper, M. K.; Veltri, C. A.; Virshup, D. M.; Ireland, C. M. *Bioorg. Med. Chem.* **2009**, *17*(6), 2189–2198.
- Gareau, Y.; Zamboni, R.; Wong, A. W. *J. Org. Chem.* **1993**, *58*, 1582–1585.