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Photocatalyzed Reduction of β-Nitroacrylates via Hydrogen Atom Transfer Promoted by Tetrabutylammonium Decatungstate

Gabriele Lupidi, Stefano Protti, Davide Ravelli,* and Alessandro Palmieri*

A photocatalyzed reduction of the C=C double bond in β-nitroacrylates under flow conditions is developed. The reaction takes place upon irradiation at 390 nm in the presence of tetrabutylammonium decatungstate and requires γ-terpinene as a hydrogen source. Products are obtained in good yields, and various functional groups are tolerated, such as unconjugated double bonds, benzyl groups and carbonyls, thus demonstrating a substantial chemoselectivity.

1. Introduction

β-Nitroacrylates **1** are organic compounds characterized by the presence of both a nitro group and an ester functionality conjugated to a double bond and positioned in a β-relationship to each other.[1] This structural feature significantly increases the electrophilicity of the double bond making these compounds valuable building blocks in organic synthesis due to their ability to undergo a wide range of transformations, particularly the construction of carbon–carbon and carbon–heteroatom bonds. In this regard, β-nitroacrylates have been employed over the years to generate highly functionalized materials and key heterocyclic systems.[2] More recently, we also discovered the high reactivity of this scaffold under both photochemical and photocatalyzed conditions. Indeed, whereas compounds **1** readily undergo *E* to *Z* photoisomerization upon direct exposure to 427 nm light (**Scheme 1**a, *path a*),[3] they also react as efficient traps toward alkyl radicals, in turn generated via photocatalyzed hydrogen atom transfer (HAT) from alkanes, amides and ethers (Scheme 1a, *path b*).[4]

In this context, tetrabutylammonium decatungstate (TBADT) is considered one of the most effective photocatalysts for the cleavage, under mild conditions, of a wide range of C—H bonds. However, in most cases, TBADT has been employed in the formation of either C—C and C-heteroatom (through halogenation, oxygenation, amination processes) bonds.[5]

Following our research program in expanding the application of TBADT,[5g,i–k] we focused on the photocatalyzed reduction of β-nitroacrylates **1** (Scheme 1b) into β-nitroesters **2**.

2. Result and Discussion

With the aim of optimizing the reaction conditions, the conversion of **1a** into **2a** in the presence of selected reducing agents was chosen as a model reaction. A series of preliminary attempts was carried out under batch conditions to find the most effective reducing agent among **3a–f** (**Table 1**).

In all cases, the starting material **1a** was fully converted within 1.5 h; nevertheless, **2a** was recovered only in moderate yields (compare the results obtained in entries 1–6), with the best outcome observed in the presence of γ-terpinene **3f** (40%). Increasing the amount of **3f** to 1.5 eq. allowed for the isolation of **2a** in 46% yield (Entry 7). On the contrary, a further increase in the concentration of the reducing agent was found noxious to the reaction outcome (Entry 8). Finally, experiments performed in the absence of TBADT (Entry 9) as well as in the dark (Entry 10) pointed out the essential role of both the photocatalyst and of light for the observed transformation. It should be noticed, however, that a complex mixture of inseparable by-products was observed in all reactions, justifying the modest mass balance observed in all the entries. At this point, to improve the reaction efficiency and minimize the formation of by-products, we turned our attention to flow chemistry conditions.

As widely reported in the literature, this enabling technology allows for a better control of reaction conditions,[6] and ensures a more uniform irradiation of the reaction mixture compared to

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G. Lupidi, A. Palmieri
Green Chemistry Group
School of Sciences and Technology
Chemistry Division
University of Camerino
ChIP Research Center
Via Madonna delle Carceri, 62032 Camerino, MC, Italy
E-mail: alessandro.palmieri@unicam.it

S. Protti, D. Ravelli
PhotoGreen Lab
Department of Chemistry
University of Pavia
Viale Taramelli 12, 27100 Pavia, PV, Italy
E-mail: davide.ravelli@unipv.it

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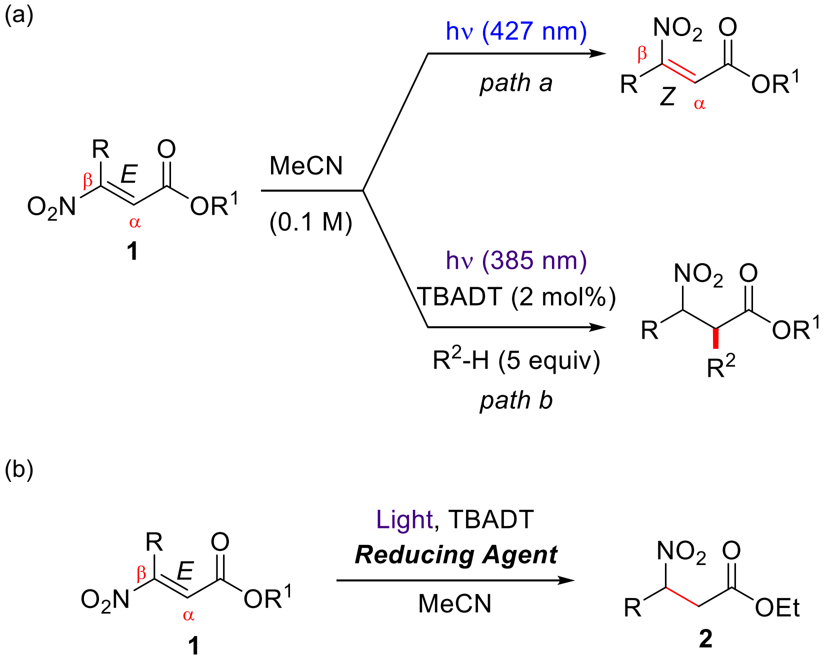
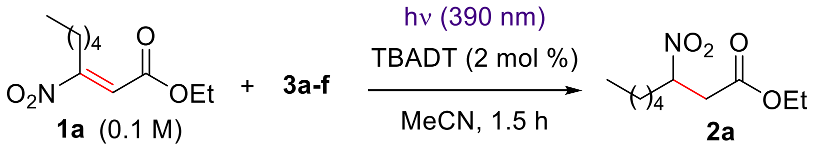
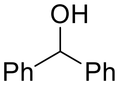
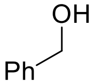
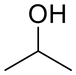
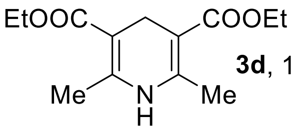
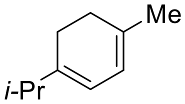
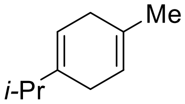


Scheme 1. Light-mediated reactions involving β-nitroacrylates: a) previous reports and b) this work.

Table 1. Screening of the reducing agent **3**.



Entry[a)]	Reducing agent 3	Yield [%] of 2a[b)]
1	 **3a**, 1.2 equiv	37
2	 **3b**, 1.2 equiv	28
3	 **3c**, 1.2 equiv	32
4	 **3d**, 1.2 equiv	33
5	 **3e**, 1.2 equiv	36
6	 **3f**, 1.2 equiv	40
7	**3f**, 1.5 equiv	46
8	**3f**, 2.0 equiv	31
9	**3f**, 1.2 equiv[c)]	0
10	**3f**, 1.2 equiv[d)]	0

[a)] Reaction performed on 0.5 mmol of **1a**; [b)] Yield of the pure isolated product; [c)] Reaction performed in the absence of TBADT; [d)] Reaction performed in dark.

batch protocols.[7] Our protocol permits as well to limit over-irradiation of **2a** once formed, which could be one of the causes for byproduct formation. The flow equipment we implemented consists of a syringe pump, containing acetonitrile used as carrier for moving the solution into the line; a 5 mL coil reactor (**R**) used as reservoir for the solution of **1a**, **3f** and TBADT; 2 three-way valves (V_1 and V_2) used for the refilling-purge of the coil; a **LTF-V** borosilicate glass reactor (R_1);[8] and a LED lamp placed at 6 cm from the reactor; and a back pressure regulator (**BPR**) set at 20 psi (**Figure 1**).

By employing this device, we repeated the reduction of **1a** into **2a** under the conditions optimized in batch (**Table 2**, Entry 1), and, with our delight, the reaction took place in a shorter time (1 h $_{flow}$ *vs* 1.5 h $_{batch}$) and afforded **2a** in 61% yield (however, the formation of a small amount of a complex mixture of inseparable by-products was still observed). We thus screened the reaction by both doubling and halving the power of the light and the concentration (Entries 2–7). Increasing the power of light to 40 W led to an even faster conversion of **1a** into **2a** (0.5 h *vs* 1 h); however, the yield of **2a** decreased to 17% (Entry 2). Conversely, decreasing the power to 10 W made the conversion completely ineffective, since only traces of product were noticed, and no improvement was observed even after prolonged photoirradiation (4 h, Entry 3). Further studies involved the concentration of the reaction mixture. In particular, doubling the concentration of **1a** resulted in a lower yield of **2a** (35%, Entry 4), while diluting the solution to 0.05 M had no significant effect on the yield (58%, Entry 5). Similarly, a shorter residence time did not ensure a full conversion of **1a**, since **2a** was obtained in just 37% yield of isolated product, whereas a longer residence time did not affect the reaction trend (Entries 6 and 7). Finally, the amount of TBADT was also assessed, however without any substantial improvement (Entries 8,9).

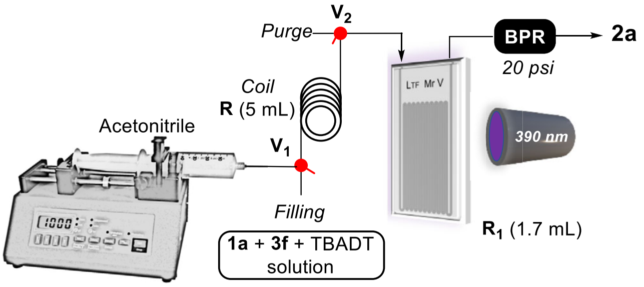
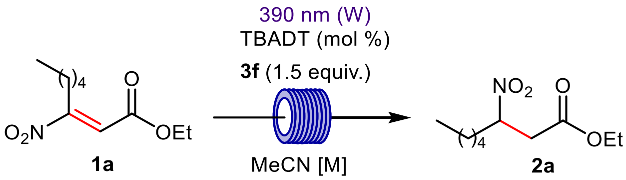


Figure 1. Scheme of the flow equipment.

Table 2. Optimization studies under continuous flow conditions.



Entry[a]	TBADT [mol%]	Residence time [h]	MeCN [M]	Light power [W]	Yield [%] of 2a[b]
1	2	1	0.1	20	61
2	2	0.5	0.1	40	17
3	2	4	0.1	10	Traces + **1a**
4	2	1	0.2	20	35
5	2	1	0.05	20	58
6	2	0.5	0.1	20	37 + **1a**
7	2	1.5	0.1	20	59
8	1	1	0.1	20	31 + **1a**
9	5	1	0.1	20	60

[a]Reaction performed on 0.5 mmol scale; [b]Yield of the pure isolated product.

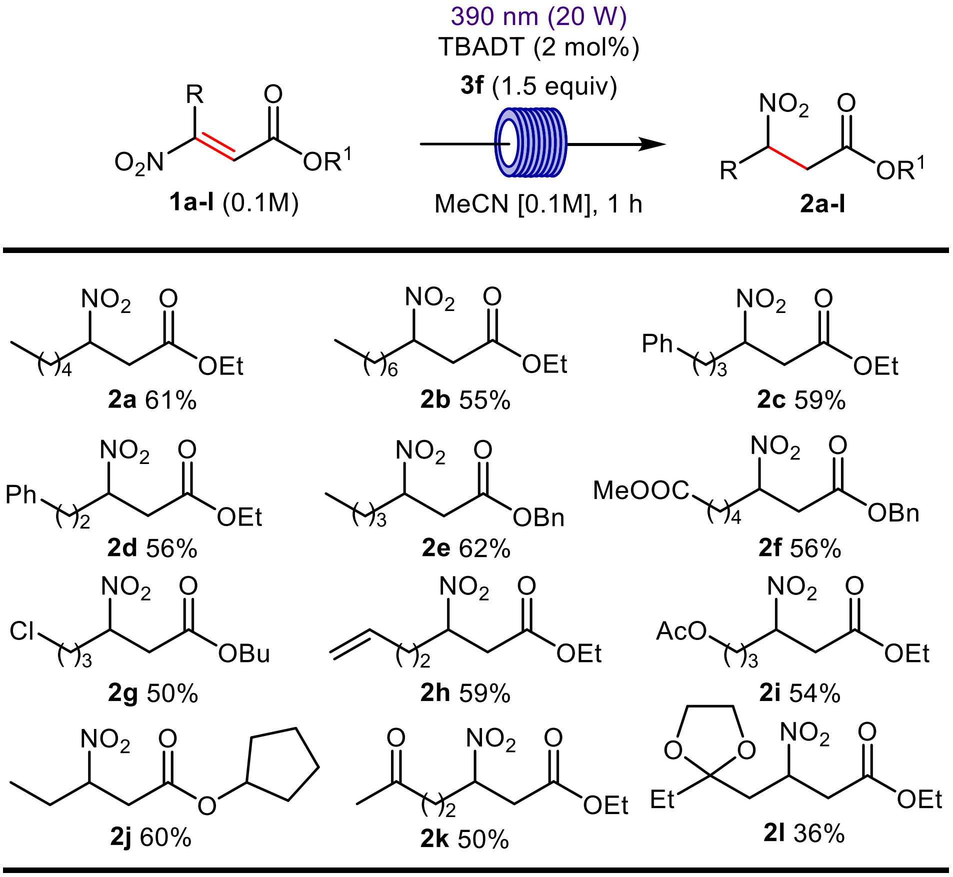
Spurred by these results and with the aim of demonstrating the general versatility of our process, we tested a variety of β-nitroacrylates **1** under the optimized reaction conditions. Products **2** were generally isolated in good yields (50%–62%), with the only exception of compound **2l**, which was isolated in a serviceable 36% yield (**Scheme 2**). In this case, the lower efficiency is probably due to the reactivity of the dioxolane ring that opens the path to competitive side reactions increasing the formation of by-products.[4]

Moreover, the mild reaction conditions allowed for the preservation of key functionalities that could be further manipulated. Thus, our approach enabled the chemoselective reduction of the electrophilic double bond, while other groups such as unconjugated double bonds, benzyl groups and carbonyls, which are typically reactive under alternative reducing conditions, were well tolerated.

Next, given the broad importance of deuterated compounds in medicinal chemistry and materials science settings,[9] we investigated the reductive deuteration of β-nitroacrylates **1** by conducting the photochemical reduction in the presence of deuterated water. Specifically, the reduction of **1a** was examined using various MeCN:D_2O mixtures (**Table 3**). Gratifyingly, all conditions yielded exclusively the deuterated compound **2a(D)** in comparable amounts. Notably, while α-mono deuteration was complete in all cases, the degree of β-deuteration increased along with the amount of deuterated water employed, resulting almost complete in an 8:2 MeCN:D_2O solvent mixture. In order to exclude any thermal proton-exchange contribution to the deuteration process, compound **2a** was dissolved in an 8:2 MeCN:D_2O mixture and stirred for 5 h; NMR analysis of the reaction crude excluded any deuteration had occurred.

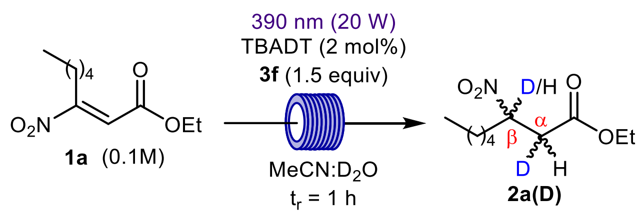
Deuteration was also carried out on β-nitroacrylates **1d** and **1h**, yielding products with complete α-monodeuteration and excellent values of β-deuteration (**Figure 2**).

From a mechanistic perspective, the process proceeds with two slightly different pathways depending on the presence or absence of deuterated water. In the latter case (**Scheme 3**a), the process is promoted by photoexcited TBADT* that abstracts



Scheme 2. Photocatalyzed reduction of β-nitroacrylates: substrate scope demonstration (5 mL scale).

Table 3. Photocatalyzed reductive deuteration of β-nitroacrylates **1**.



Entry[a]	MeCN:D_2O	α-mono deuteration [%]	β-deuteration [%]	Yield [%] of 2a(D)[b]
1	95:5	100	79	60
2	9:1	100	89	59
3	8:2	100	≈94	61

[a] Reaction performed on 0.5 mmol scale; [b] Yield of the pure isolated product.

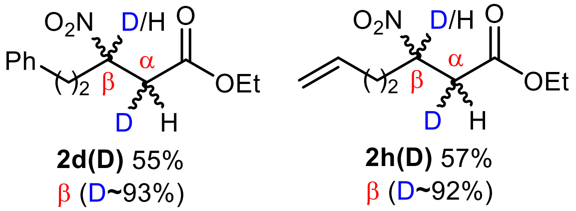
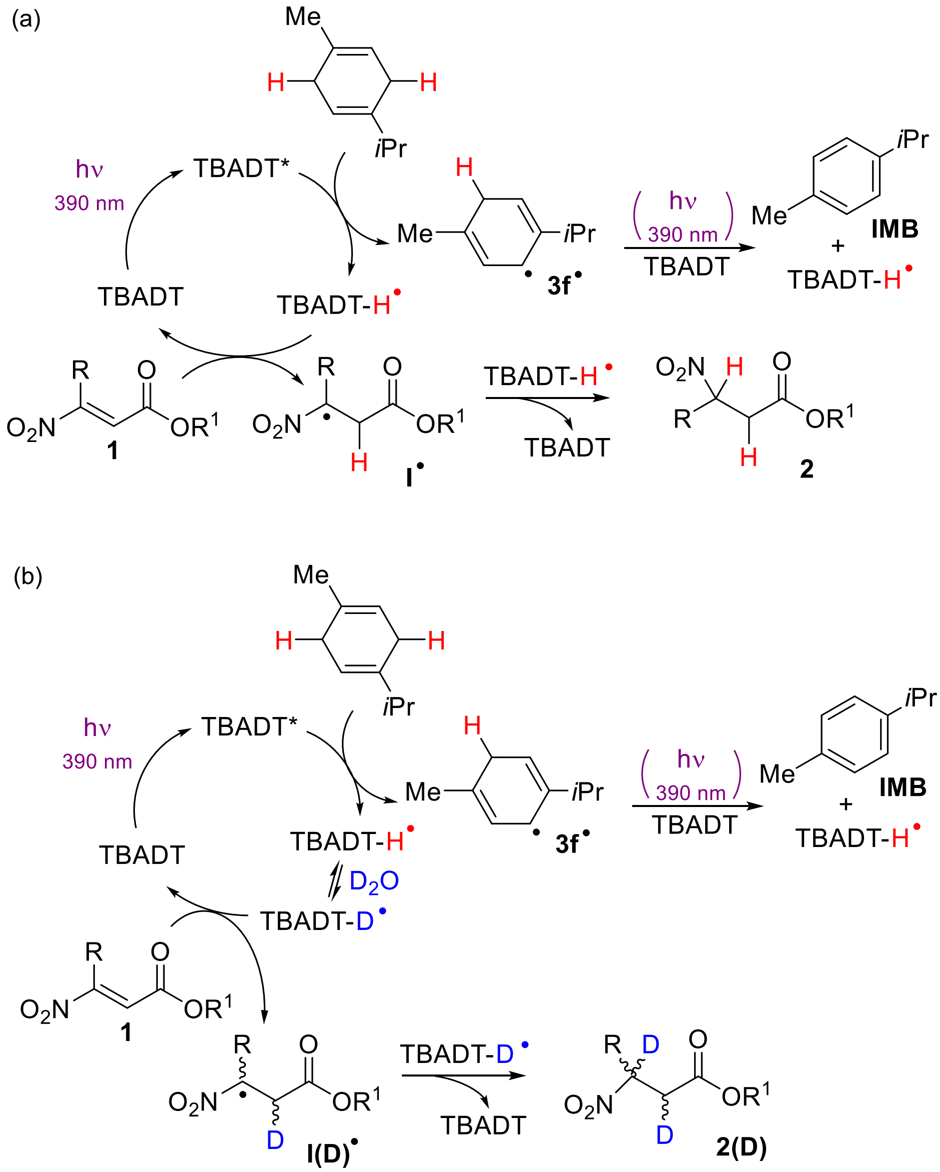


Figure 2. Percentage of deuteration for compounds **2d(D)** and **2h(D)**.

a hydrogen atom from γ-terpinene **3f** producing the cyclohexadienyl-type radical **3f**$^{\bullet}$ and reduced TBADT-H$^{\bullet}$, which in turn transfers a hydrogen atom to β-nitroacrylates **1** forming *C*-centered radicals **I**$^{\bullet}$. Simultaneously, the radical intermediate **3f**$^{\bullet}$ reacts with a new molecule of TBADT (possibly aided by an additional excitation step) affording another equivalent of TBADT-H$^{\bullet}$ along with isopropyl methyl benzene (**IMB**) as the coupled product. Finally, radicals **I**$^{\bullet}$ in turn react with TBADT-H$^{\bullet}$ yielding the reduced products of interest **2**.

In the presence of deuterated water (D_2O) as the co-solvent (Scheme 3b), a deuteron (D^+) is exchanged between D_2O and TBADT-H$^{\bullet}$ providing TBADT-D$^{\bullet}$, as already documented in the literature.[10] The latter species in turn transfers a deuterium atom to β-nitroacrylates **1** forming radicals **I(D)**$^{\bullet}$, which in turn incorporate an additional deuterium atom through a mechanism analogous to that described above and afford the



Scheme 3. Proposed reaction mechanism.

deuterated product **2(D)**. Competition between TBADT-D$^\bullet$ and residual TBADT-H$^\bullet$ is responsible for the incomplete deuteration in β-position of **2**.

3. Conclusion

In conclusion, we have developed an efficient and practical method for the reduction of β-nitroacrylates to the corresponding β-nitro esters through a photocatalyzed hydrogen atom transfer (HAT) strategy. This protocol provides the desired products in satisfactory yields and short reaction times. Moreover, the mild reaction conditions and the high chemoselectivity of the HAT process ensure a good functional group tolerance. Finally, by the simple addition of deuterated water to the system, it has been possible to smoothly prepare deuterated molecular structures, which are suitable for further manipulation.

4. Experimental Section

General Remarks

^{1}H NMR analyses were recorded at 400 MHz on a Varian Mercury Plus 400. ^{13}C NMR analyses were recorded at 100 MHz. IR spectra were recorded with a Perkin Elmer FTIR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. GS-MS analyses were obtained on a Hewlett-Packard GC/MS 6890 N that works with the EI technique (70 eV). Solutions in the flow apparatus were injected using syringe pumps model NE-300 (New Era Pump Systems Inc.) LTF-V microreactor (I.D. channel 1 mm; volume reactor 1.7 mL) was purchased by Little

Things Factory GmbH.[8] Photochemical irradiation was performed by using 40 W Kessil lamp (emission centered at 390 nm).[11]

General Procedure for the Synthesis of Compounds 2a-l

A 0.1 M solution of the appropriate β-nitroacrylate **1** in acetonitrile containing 2 mol% of TBADT and 1.5 equiv. of **3f** was first purged with argon and then transferred into the coil reservoir **R** by valves $\mathbf{V_1}$ and $\mathbf{V_2}$ (see Figure 1). Successively, the solution was pumped with a flow rate of 1.133 mL h^{-1} into the LTF-V microreactor $\mathbf{R_1}$ irradiated at 390 nm (lamp placed at 6 cm working at 20 W, 50% of power) and pressurized by a **BPR** set at 20 psi. The outflow was collected in a 25 mL round bottom flask; the solution was concentrated at reduced pressure to give the crude product **2** which was purified by flash column chromatography.

The deuteration reactions were carried out using the same protocol but replacing pure MeCN with 0.1 M solutions of MeCN and D_2O in the indicated proportion.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: β-nitroacrylates · flow chemistry · hydrogen atom transfer · photocatalysis · reduction

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[11] The complete emission spectra are available at the link: https://kessil.com/products/science_PR160L.php.

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