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Microwave-Promoted Pd-Catalyzed Cyanation of Aryl Triflates: A Fast and Versatile Access to 3-Cyano-3-desoxy-10-ketomorphinans

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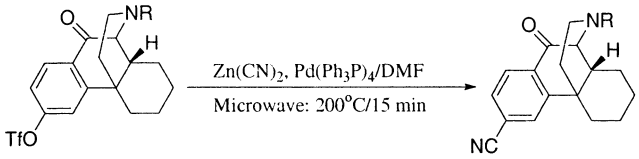
ABSTRACT



A methodology for the microwave-promoted conversion of triflates to the corresponding nitriles by using 8% equiv of $Pd(Ph_3P)_4$ as the catalyst and 2.0 equiv of $Zn(CN)_2$ as the cyanide source has been developed. This method is highly efficient for the preparation of 3-cyano-3-desoxy-10-ketomorphinans. The reaction was generally completed in 15 min at 200 °C and produced products in greater than 86% yields.

Nitriles are valuable intermediates in organic synthesis and can be transformed to produce a variety of functionalities including amide, thiazole, oxazolidone, triazole, and tetrazole.[1] In the course of our studies on the design and synthesis of novel ligands for opioid receptors, we became interested in 3-cyano-3-desoxy-*N*-alkyl-10-ketomorphinans **2**, which can be recognized as important precursors for a series of opioid receptor agonists/antagonists.[2] Various methods have been reported for the formation of nitriles including the stoichiometric reaction of aryl halides with copper(I) cyanide, the Reissert−Henze cyanation of π-deficient heteroarene *N*-oxides, the electrophilic cyanation of π-excessive heteroaromatics, and transition-metal-catalyzed displacement of aryl halides with cyanide ion.[3,4] An alternative route to aryl cyanides is the displacement reaction of aryl triflates with sodium or potassium cyanide catalyzed with palladium(0) or nickel(0). These methods achieved limited success.[5]

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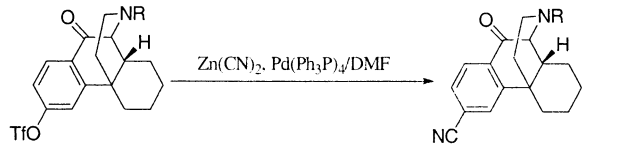
Recently, the reagent system composed of zinc cyanide and catalytic palladium tetrakistriphenylphosphine in DMF was reported to be a general and efficient system for cyanation of aryl bromides and aryl triflates.[6,7] This method has been successfully applied to the synthesis of 3-cyano-3-desoxynaltrexone from the corresponding triflate.[8]

To achieve the synthesis of nitrile **2**, which was a key immediate for a series of κ opioid receptor selective agonists/antagonists, we first tried the reagent system of zinc cyanide and catalytic $Pd(Ph_3P)_4$ in DMF by thermal heating (Scheme 1). Under the same conditions reported by Rice,[8] triflate **1a**

Scheme 1



1a (R = *c*-$C_4H_7CH_2$)
1b (R= CH_3)

2a (R = *c*-$C_4H_7CH_2$)
2b (R= CH_3)

was converted to nitrile **2a** in 60% yield. Higher temperatures and longer reaction times did not give better yields. In the case of triflate **1b**, no or little product was obtained, even at 200 °C or with LiCl as the additive (Table 1).

Table 1. Thermal Heated Cyanation Reaction with Aryl Triflate

triflate	$Zn(CN)_2$ (equiv)	$Pd(Ph_3P)_4$ (equiv)	time (h)	*T* (°C)	additive	yield (%)
1a	2	4%	10	120	–	60[a]
1a	2	4%	24	150	–	58[a]
1b	2	4%	24	150	–	0[b]
1b	2	4%	24	200	–	<5[b]
1b	2	4%	12	200	LiCl	<5[b]

[a] Isolated yields. [b] Determined by HPLC.

Automated and focused microwave flash heating has recently proven to be very effective in accelerating organic transformations and has been widely applied in parallel synthesis and in drug discovery processes. Numerous successful reactions with great efficiency and dramatically enhanced reaction rates have been disclosed.[9] Hallberg[7] recently reported the cyanation of aryl and vinyl bromides with microwave irradiation as the energy source, but there are no reports on the preparation of nitriles from the corresponding aryl triflates[10,11] under microwave-assisted conditions. Therefore, we believe we are the first to report that flash heating by microwave irradiation assists the formation of nitriles **2** from the triflates **1**.

As a starting point for the development of our microwave-mediated methodology, we chose the cyanation of triflate **1a** as the model reaction. During the formation of 3-cyano-3-desoxynaltrexone from the corresponding triflate under thermal heating, Rice[8] reported the best result was obtained by using 2 equiv of $Zn(CN)_2$ and 4% equiv of $Pd(Ph_3P)_4$ at 120 °C. We employed this condition directly to our microwave-mediated reaction. The effect of varying temperatures and time was investigated and the results are summarized in Table 2. We found that by using 2 equiv of $Zn(CN)_2$ and 4% equiv of $Pd(Ph_3P)_4$ at 200 °C, it was possible to obtain 90% yield after 15 min of microwave irradiation (Run 5). A decrease of $Zn(CN)_2$ resulted in a decreased yield (Run 6), while an increase of $Pd(Ph_3P)_4$ enhanced the yield (Run 7), which was recognized as the best conditions in our investigation.[12]

Table 2. Optimization of Microwave-Assisted Cyanation Reaction with Aryl Triflate **1a**

run	$Zn(CN)_2$ (equiv)	$Pd(Ph_3P)_4$ (equiv)	time (min)	*T* (°C)	yield (%)[a]
1	2	4%	1	150	0
2	2	4%	2	200	5
3	2	4%	5	200	50
4	2	4%	10	200	85
5	2	4%	15	200	90
6	1	4%	15	200	70
7	2	8%	15	200	94

[a] Yield was determined by HPLC.

A variety of 10-ketomorphinan triflate analogues **1** with different N-substituents were investigated under the optimized reaction conditions. From the results shown in Table 3, this methodology is applicable to a wide range of *N*-alkyl 10-ketomorphinan triflate substrates **1** to afford products with yields of 86−92% in 15 min. The method is extremely efficient for the cyanation of triflate **1b**, which was unsuc-

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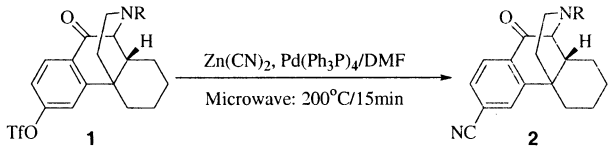
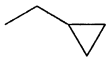
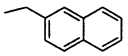
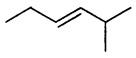
Table 3. Microwave-Assisted Cyanation Reaction with Aryl Triflate **1**

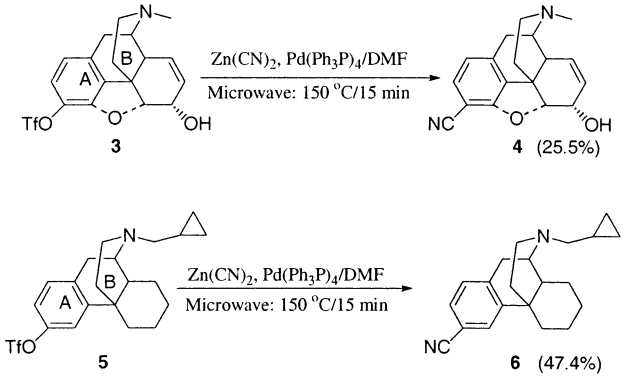


triflate	R =	product	isolated yield
1a		**2a**	92.4 %
1b	Me	**2b**	89.5 %
1c		**2c**	89.0 %
1d	Ph	**2d**	87.4 %
1e		**2e**	88.3 %
1f		**2f**	86.3 %
1g	OMe	**2g**	86.6 %

cessful using traditional heating conditions, while a yield of 89.5% was achieved in microwave-promoted heating.

To explore the extent of this reaction, we applied this methodology to the cyanation of triflates **3** and **5** (Scheme 2). Surprisingly, in both cases without a keto group attached

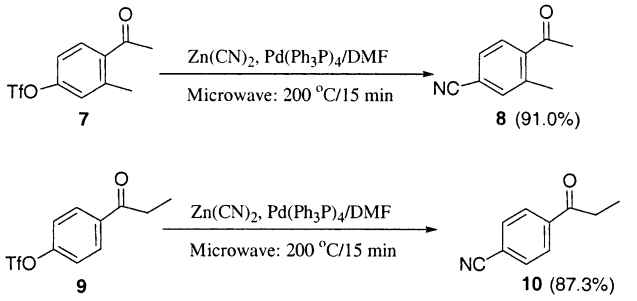
Scheme 2



to the B ring, poor yields were observed. In the case of triflate **3**, the reaction system was very complicated under microwave irradiation at 200 °C for 10 min, while at 150 °C for 15 min, the nitrile **4** was isolated in 25.5% yield with recovery of some starting material. This also occurred with triflate **5**, where nitrile **6** was isolated in 47% yield at a lower temperature (150 °C). A longer reaction time did not improve the yield and some other unknown products were detected by HPLC.

From these results, it appears that the presence of a keto group adjacent to the phenyl ring in the substrates is important for the conversion of triflate to the corresponding nitrile under microwave heating. This was further shown by the cyanation of 3-methyl-4-acetylphenyl triflate **7** and 4-propionylphenyl triflate **9**, which gave 91% and 87.3% yields, respectively (Scheme 3).

Scheme 3



In conclusion, we have developed a fast and convenient microwave-assisted, high-speed method for the displacement of triflate by cyanide ion with $Pd(Ph_3P)_4$ as the catalyst and $Zn(CN)_2$ as the cyanide source. This method is highly efficient for the preparation of 3-cyano-3-desoxy-10-keto-morphinans **2**, as well as the aryl nitriles with a keto group adjacent to the aryl ring. The mechanism elucidating the required presence of a keto group in the triflate and further application of this methodology to other substrates are under investigation.

Acknowledgment. We thank the National Institute on Drug Abuse (NIDA) for financial support (DA 40595) and Dr. Wennan Xiong for the preparation of triflate **5**.

Supporting Information Available: Full experimental details for all transformations and the analytical characterization of all new compounds are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Procedure.** Microwave irradiation in a Smith Synthesizer was used to rapidly increase the temperature to 200 °C. In a 10-mL glass tube were placed triflate (0.2 mmol), $Zn(CN)_2$ (47 mg, 0.4 mmol), $Pd(Ph_3P)_4$ (19 mg, 0.016 mmol), 5 mL of DMF, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation was used and the temperature was rapidly increased from room temperature to 200 °C. Once 200 °C was reached, the reaction mixture was held at this temperature for 15 min and then cooled rapidly to room temperature. The reaction vessel was opened and the contents were poured into a separating funnel. Saturated sodium carbonate and water were added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The extracts were combined, washed with brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography to yield the nitrile compounds.