

Optimising the Mizoroki-Heck reaction of cyclic allyl amines: gram-scale synthesis of Preclamol without protecting groups

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Abstract. Though a widely used metal-catalysed cross-coupling process, the Mizoroki-Heck ('MH') reaction can be a capricious transformation. This is particularly true for oxidation-prone alkene substrates containing ligating heteroatoms, as in the case of *N*-alkyl tetrahydropyridines whose MH reactions have been under-explored, due to the many side-reactions which hamper the process. Since the products of tetrahydropyridine Heck reactions are direct precursors to potent pharmacophores, and therefore of commercial value, this is a significant drawback and limitation. We report here the results of our study designed to deliver an optimized, scalable MH procedure for *N*-alkyl tetrahydropyridines, and its exemplification in a gram-scale synthesis of the drug substance Preclamol.

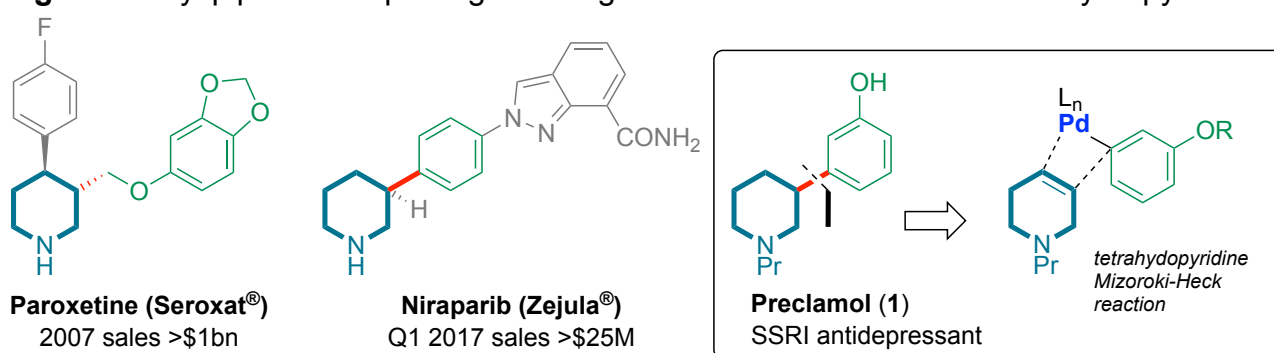
Keywords. Catalysis, tetrahydropyridines, Mizoroki-Heck reaction, aryl piperidines, CNS drugs.

1. Introduction

Amongst the many catalytic processes available to the modern synthetic chemist, the Mizoroki-Heck ('MH') reaction¹ is of special significance as the first reported method² which enabled direct, substoichiometric catalytic modification of simple alkenes: the overall transformation is effectively a CH activation process, in which an aryl unit is inserted into an sp²-CH bond (Scheme 1). The reaction has been intensely studied and optimised, and a wide range of coupling partners (aryl halides, triflates, sulfonates, diazonium salts, iodonium salts), alkenes and catalysts has been used productively in the process, with many successful applications to the production of complex natural and synthetic targets.³ Notwithstanding the proven synthetic power of the transformation, there are several known limitations to the process; thus, the reactions are often heterogeneous (precluding detailed kinetic and mechanistic analysis), and some alkene classes are unreliable and capricious substrates. Unsaturated amines fall into this category, often undergoing inefficient transformations which require high substrate or catalyst loading; this is especially the case

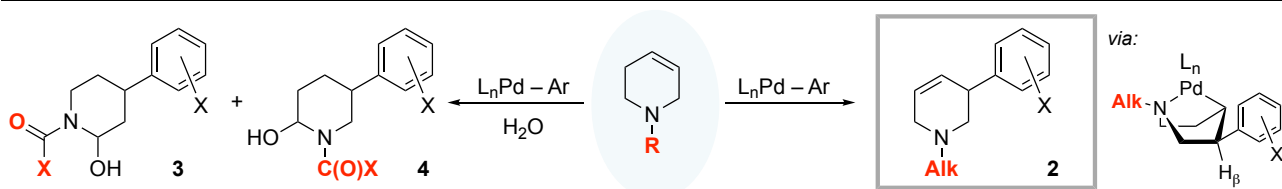
for cyclic allyl amines (such as tetrahydropyridines⁴, and pyrrolines⁵), which react efficiently only if the lone-pair of electrons on nitrogen is delocalized into an electron-withdrawing protecting group. This limitation is a particular drawback, since the method in theory allows for direct synthesis of N-alkyl piperidines and pyrrolidines, a class of heterocycle with privileged pharmacological status, particularly in CNS-active compounds such as the marketed drugs paroxetine⁶ and niraparib⁷ (Figure 1); however, to date, the limitations of MH reaction of tetrahydropyridines (lack of regioselectivity, over-reaction, multiple isomerisation pathways and low yields) have severely restricted the use of this potentially impactful catalytic process.

Figure 1. Aryl piperidines: privileged biological motifs accessible from tetrahydropyridines



3-Aryl piperidines are a class of heterocycle with particular biological potency, and Preclamol⁸ occupies a pre-eminent position as a first-in-class antipsychotic drug substance. The compound is a dopamine autoreceptor agonist, and it has been used in man for the treatment of schizophrenia.⁹ To access this compound, and other related biologically active compounds, a range of heterocycles can function as chemical feedstocks for catalytic processing (Figure 2).

Figure 2. Catalytic strategies for the synthesis of Preclamol

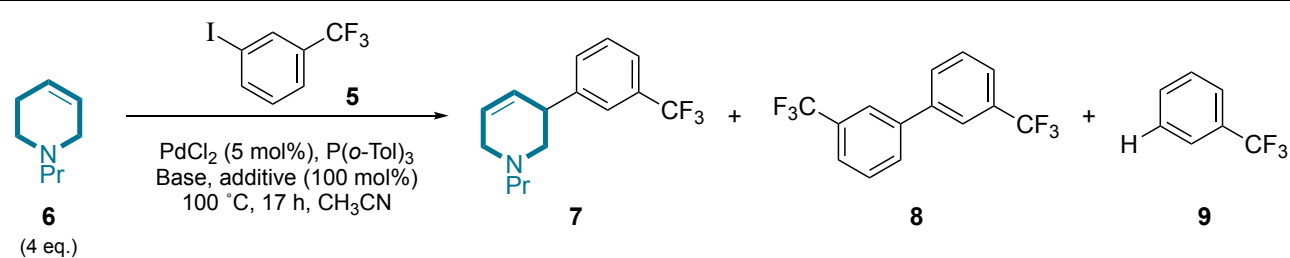


Given the ready commercial availability of *N*-alkyl tetrahydropyridines, and the great utility of 3-arylpiperidines, we undertook a study of the factors affecting these complex MH reactions, and report an improved and simplified synthesis of Preclamol using our new method.

2. Results and discussion

Our project had three key aims: firstly, to reduce the catalyst loading for MH reaction to ≤ 1 mol%; secondly, to avoid the use of a silver additive; thirdly, to develop a method involving no protecting groups. In particular, the latter goal was a demanding one, due to the known challenges in using phenols in palladium-catalysed reactions,¹⁶ but was one which offered significant mass balance advantages if successful.

Table 1: Initial optimisation of the Mizoroki-Heck reaction of tetrahydropyridine **6**



Entry	P(<i>o</i> -Tol) ₃ /mol%	Base	Additive	Conversion/%	Yield/%		
					7	8	9
1	20	-	AgNO ₃	100	18 ^a	16	62
2	40	-	AgNO ₃	100	10	9	78
3	10	-	AgNO ₃	100	27	10	49
4	5	-	AgNO ₃	100	35	11	42
5	5	DMPip ^b (5 eq.)	AgNO ₃	92	39	3	16
6	5	DMPip (1 eq.)	AgOTf	100	49	7	19
7	5	DMPip (5 eq.)	Cu(OTf) ₂	100	55	3	6
8	7.5	DMPip (1 eq.)	Cu(OTf) ₂	100	59	3	11
9	5	DMPip (1 eq.)	Cu(OTf) ₂	100	58	2	8
10	7.5	DMPip (1 eq.)	(CuOTf) ₂ •PhCH ₃	98	58	4	12

11	7.5	DMPip (1 eq.)	Zn(OTf) ₂	100	52	2	28
12	7.5	DMPip (5 eq.)	Zn(OTf) ₂	100	61	2	10

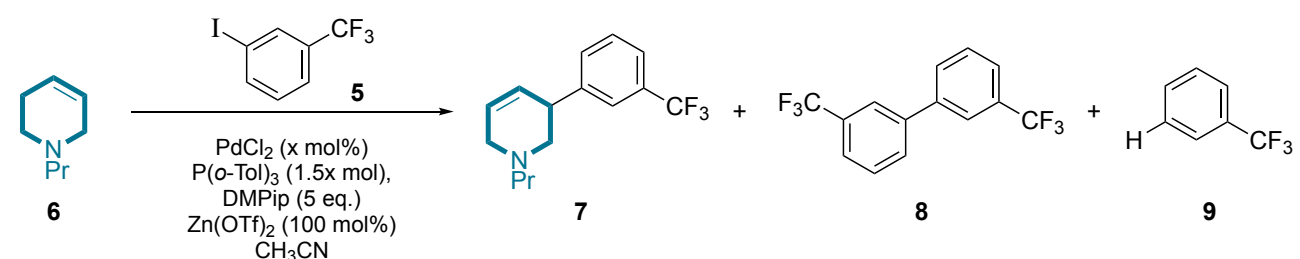
^a Yields estimated from ¹⁹F NMR spectra; ^b *N,N*-dimethylpiperazine

Preliminary studies of the *N*-alkyl THPy Mizoroki-Heck reaction confirmed the limitations of the reaction: the heterogeneous process delivered a multitude of products in addition to the desired arylated target, predominantly pyridinium species (and derived compounds) arising from metal-catalysed oxidation. We therefore embarked upon a detailed analysis of the parameters of this reaction (Pd catalyst, ligand, base, solvent, additive, temperature); to simplify the analysis of this complex reaction, we chose (3-iodo)benzotrifluoride **5** as a model substrate, using ¹⁹F NMR to study its reaction with *N*-propyl tetrahydropyridine **6**. In this manner, we hoped to optimise the yield of the target product (**7**), and quickly identify and quantitatively estimate the side-product profile of the reaction, thus giving valuable insights into the reaction mechanism and facilitating optimisation. A summary of the salient data obtained from the initial optimisation phase is given in Table 1.

The next phase of optimisation was focused on improving the efficiency of the transformation, by reducing the loadings of catalyst and substrate, and on the reaction temperature (Table 2).

Satisfyingly, the use of 1 mol% PdCl₂ was effective without reducing the yield of **7** (Table 2, entry 3), though a 0.5% catalyst loading was less efficient (Table 2, entry 2). Variation in the stoichiometry of tetrahydropyridine had a less pronounced effect on the reaction, with a 50% decrease in loading having little negative impact on the yield of **7** (Table 2, entry 5). Finally, lowering the temperature to 70 °C proved to have a positive effect on the yield (Table 2, entries 7 and 8).

Table 2: Optimisation of MH reaction of **6**: influence of temperature, catalyst loading and stoichiometry



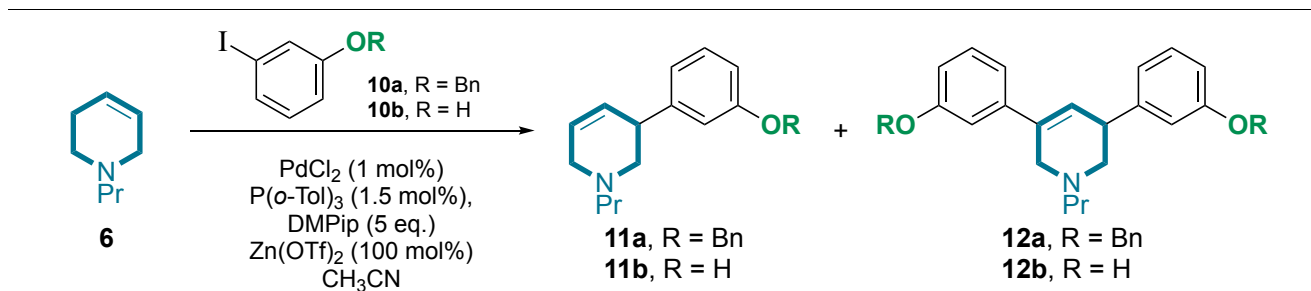
Entry	PdCl ₂ / mol%	5 /eq.	Temperature (°C)	Time (h)	Conversion	Yield/%		
						7	8	9

1	5	4	100	17	100	61 ^a	2	10
2	0.5	4	100	17	95	56	2	10
3	1	4	100	17	100	60	1	9
4	5	3	100	17	100	63	2	9
5	5	2	100	17	100	59	3	8
6	5	1.5	100	17	100	56	4	8
7	1	3	70	120	100	67	1	6
8	1	2	70	120	100	62 (55 ^b)	2	6
9	1	1.5	70	120	89	57	1	5

^a Estimated from ¹⁹F NMR spectra ^b isolated yield (5 mmol scale reaction)

Armed with an optimised procedure, we turned to the synthesis of Preclamol, and observed that using either benzyl ether **10a** or free phenol **10b**, MH reactions were significantly improved compared to the previously reported procedure: in particular, **11b** was obtained in 55% yield, compared to 28% reported by Hallberg *et al.* (Table 3, entry 3). In addition to the desired product **11a** and **11b**, on the larger scale of these reactions, we now also detected the presence of novel diarylated alkenes **12a** and **12b**.

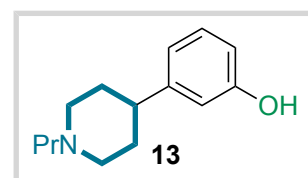
Table 3: Optimised MH reaction of **6**



Entry	6 (eq)	R	Yield 11 /%	Yield 12 /%
1	4	Bn	11a , 55 ^a	12a , 5 ^b
2	2	Bn	11a 49	12a , 13
3	4	H	11b , 55 ^c	12b , 6
4	2	H	11b , 49	12b , 10

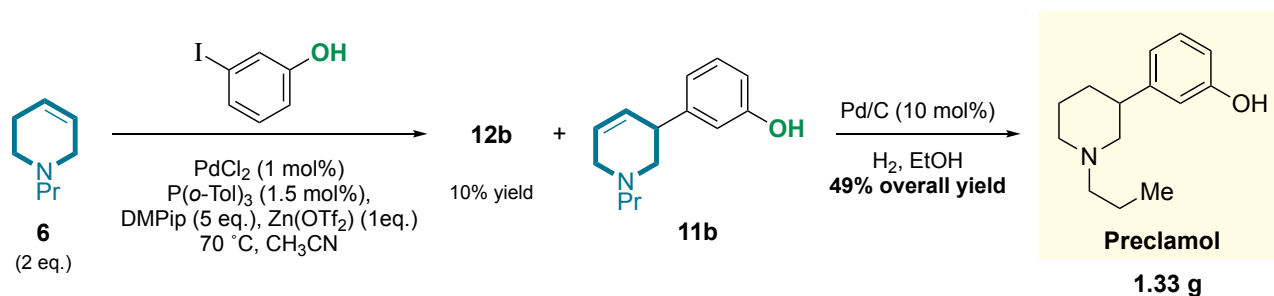
Isolated yield, 5 mmol scale; ^b Estimated from ¹H NMR; ^c 12.5 mmol scale.

When performed on a 12.5 mmol scale (Scheme 1), the extent of side-reactions involved in MH reactions of *N*-alkyl tetrahydropyridines becomes apparent, with side-products derived from other possible palladium σ -intermediates: thus in addition to **11b**, and diarylated amine **12b**,



Preclamol (**1**) itself and saturated amine **13** were observed in small amounts, the latter products presumably formed via reductive MH processes.¹⁷ Hydrogenation of either **11a** or **11b** gave Preclamol in 49-55% overall yield.

Scheme 1. Improved synthesis of Preclamol **1**



3. Conclusion

In summary, we have designed and implemented an improved method for the Mizoroki-Heck reaction of *N*-propyl tetrahydropyridine, which is more cost-effective, milder, more functional group tolerant, and which efficiently provides access to gram quantities of Preclamol in good overall yield. Developing an in-depth understanding of the detailed mechanistic features of this complex heterogeneous catalytic reaction is a focus of our current research.

4. Materials and methods

Full experimental details and key spectra for products can be found in the Supplementary Material.

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