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# Diversification of edaravone via palladium-catalyzed hydrazine cross-coupling: Applications against protein misfolding and oligomerization of beta-amyloid

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ABSTRACT

*N*-Aryl derivatives of edaravone were identified as potentially effective small molecule inhibitors of tau and beta-amyloid aggregation in the context of developing disease-modifying therapeutics for Alzheimer's disease (AD). Palladium-catalyzed hydrazine monoarylation protocols were then employed as an expedient means of preparing a focused library of 21 edaravone derivatives featuring varied *N*-aryl substitution, thereby enabling structure–activity relationship (SAR) studies. On the basis of data obtained from two functional biochemical assays examining the effect of edaravone derivatives on both fibril and oligomer formation, it was determined that derivatives featuring an *N*-biaryl motif were four-fold more potent than edaravone.



Alzheimer's disease (AD) is a progressive neurodegenerative disorder, leading to cognitive impairment, memory loss and ultimately dementia.[1] Currently, more than 25 million people worldwide are afflicted with AD, a number that will quadruple by 2050.[2,3] While current treatments offer temporary, symptomatic improvement, 'curative' therapies that can arrest the progression of AD are currently unavailable. The aberrant misfolding and aggregation of beta-amyloid (Aβ), arising from cleavage of amyloid precursor protein, is central to the pathogenesis of AD.[1,2,4] Accordingly, the development of drug-like small molecules that can penetrate the blood–brain barrier and interfere with Aβ aggregation, thereby inhibiting the assembly of neurotoxic oligomers, represents a promising disease-modifying therapeutic approach.

As part of our on-going research program to evaluate known drug-like molecular platforms as putative therapeutics against protein misfolding, we identified multiple chemotypes that included *N*-aryl pyrazolones such as edaravone (**1**, Scheme 1). The neuroprotective characteristics of edaravone are well-described; the potent anti-oxidant and free-radical scavenging properties of this compound have been exploited therapeutically to reduce neuronal damage associated with acute brain ischemia.[5] Moreover, since oxidative stress is known to figure prominently in the pathogenesis of AD,[6] we became interested in preparing and assessing the anti-aggregation properties of edaravone and related analogs.

In preliminary work, *N*-aryl substituents emerged as a key pharmacophore, and therefore an important locale for diversification and structure–activity relationship (SAR) studies. Whereas structural modification at the R position can be achieved by use of established methods and commercial reagents (Scheme 1), variation at the $sp^2$-hybridized *N*-aryl position requires access to structurally diverse monoaryl hydrazine synthons of the aryl-$NHNH_2$ type. Conventional protocols employed for the formation of monoaryl hydrazines include nucleophilic aromatic substitution involving an activated aryl halide,[7] as well as diazotization of aniline derivatives followed by reduction of the resulting diazonium salt.[8] While feasible,[9] such protocols can be viewed as being problematic in terms of limited substrate scope, harsh reaction conditions, and poor atom economy.

*Abbreviations:* AD, Alzheimer's disease; Aβ, amyloid beta; ThT, Thioflavin T; bio-$Aβ_{42}$, *N*-α-biotinyl-Aβ (1–42); SAR, structure activity relationship; OFB, oligomer formation buffer.

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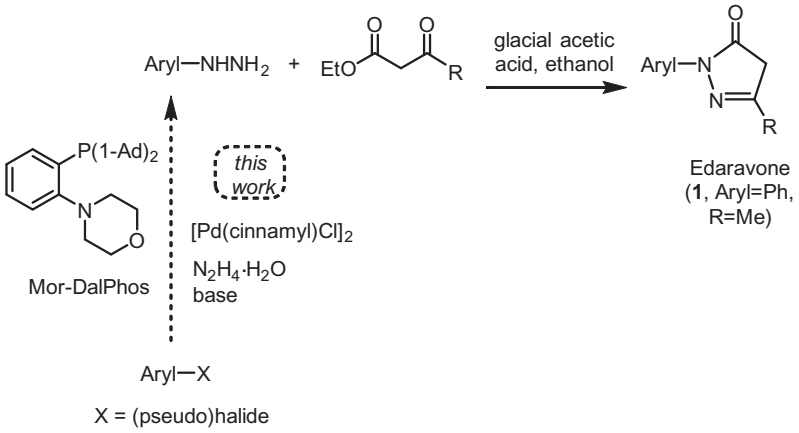


**Scheme 1.** Synthetic route to edaravone and related *N*-aryl derivatives.

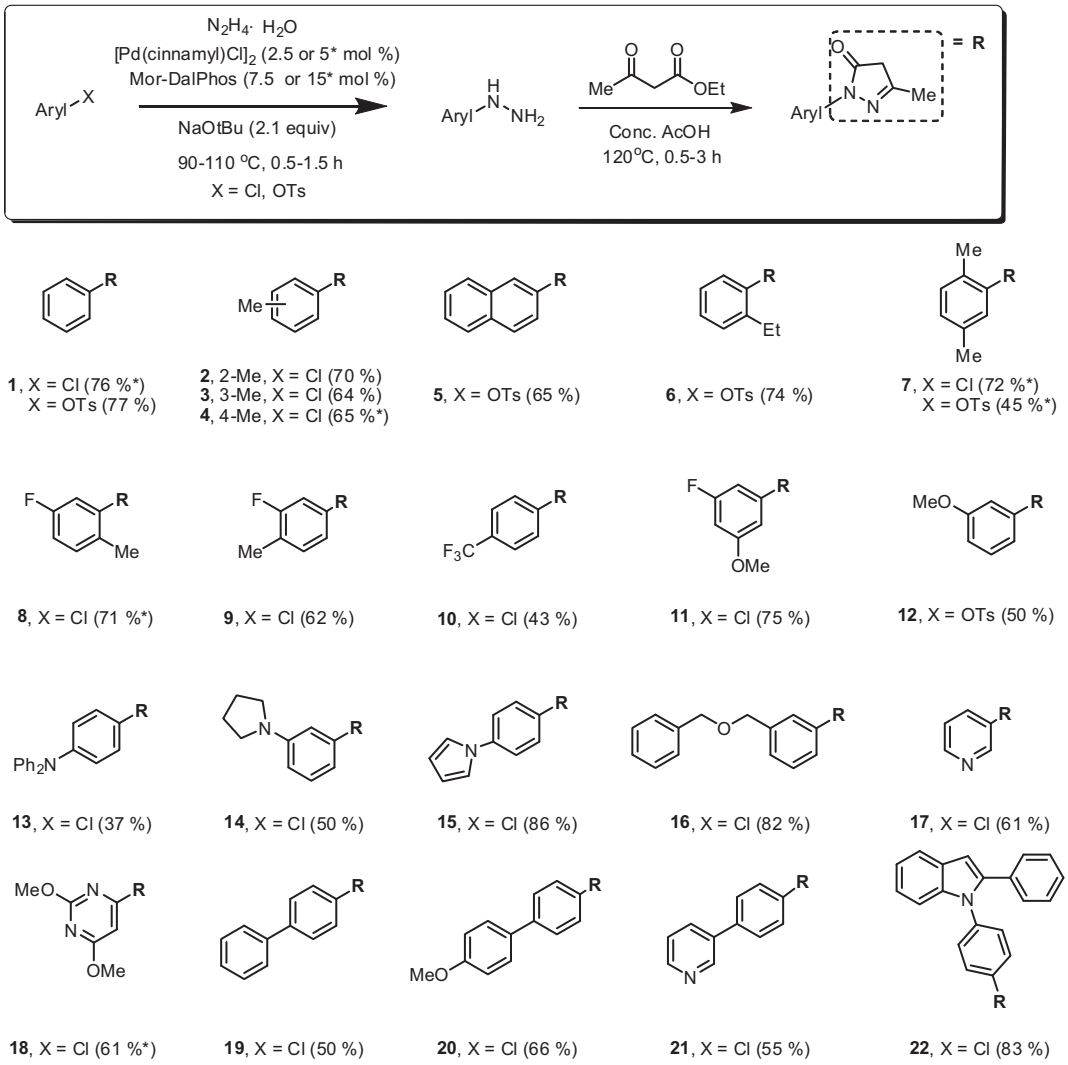


**Figure 1.** Preparation of edaravone derivatives employing palladium-catalyzed hydrazine cross-coupling methodology.

Given the broad utility of monoaryl hydrazines in the assembly of myriad heterocyclic scaffolds,[10] the identification of modular synthetic methods for the preparation of such synthons directly from (hetero)aryl (pseudo)halides and convenient hydrazine sources (e.g., $N_2H_4{\cdot}H_2O$) represents an important synthetic challenge that until very recently remained unaddressed.[11] Whereas Buchwald–Hartwig amination methods would appear to be well-suited for (hetero)aryl hydrazine synthesis, the strongly reducing nature of hydrazine presents a formidable challenge, both with respect to unwanted hydrodehalogenation of the (hetero)aryl (pseudo)halide