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Redox-Neutral α -Arylation of Amines

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Abstract

The direct α -arylation/*N*-alkylation of cyclic amines was achieved in a redox-neutral fashion under mild conditions. Transformations occur in the absence of any additives or are promoted by simple carboxylic acids.

Redox-neutral¹ approaches to the α -functionalization of amines offer attractive alternatives to the more prevalent oxidative variants.² With regard to the mechanism of these reactions, the majority of redox-neutral amine α -functionalizations involve hydride-shifts or sigmatropic H-transfer steps.³ As part of a broader effort, our group has developed a number of reactions in which amine α -functionalization is accomplished via a different approach that features azomethine ylides as reactive intermediates (Scheme 1).^{4,5,6} Here we report a strategy that enables the redox-neutral α -arylation of simple cyclic amines.

Our approach to the redox-neutral α -functionalization of amines involves the condensation of a secondary amine (e.g., pyrrolidine) with an aldehyde to give intermediates **1/1'** (Scheme 1). These species undergo redox-isomerization via azomethine ylide **3** to provide intermediates **4/4'** which are ultimately captured with a nucleophile HNu to yield α -functionalized amine **5**. The difficulty in realizing such transformations lies in the well-established propensity of species **1/1'** to undergo classic organic reactions (e.g., Strecker, Mannich, Kabachnik-Fields reaction, Friedel-Crafts alkylation, alkynylation, etc.). In previous work, we have successfully averted the classic reaction pathway by employing appropriate catalysts such as carboxylic acids or copper carboxylates in combination with sterically demanding aldehydes (e.g., 2,6-dichlorobenzaldehyde, mesitaldehyde). In favorable cases (α -cyanation^{4f} and α -phosphine oxide formation^{4j}) compounds **2** can undergo equilibration to the apparently thermodynamically more stable regioisomers **5**. This finding enabled the use of simple aromatic aldehydes as reaction partners.

We commenced our efforts toward the development of a redox-neutral amine α -arylation^{7,8,9,10,11} by exposing a mixture of pyrrolidine, 2,6-dichlorobenzaldehyde, β -naphthol and benzoic acid (20 mol %) to reflux in toluene (Scheme 2). Remarkably, the

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

reaction was extremely facile and complete consumption of the aldehyde was noted after 15 min. However, the desired product **5a** was obtained in only 22% yield. In addition, products **6** and **7** were isolated in 22% and 33% yield, respectively. The formation of both **6** and **7** is consistent with the intermediacy of enamines and other species that would be expected along the path to 1,3-dibenzyl pyrroles.^{5a} Notably, the “classic” Friedel-Crafts product **2a** was not observed under these conditions. We hypothesized that a consistently low concentration of aldehyde might prevent the formation of undesired byproducts. Consequently, a number of experiments were performed in which the aldehyde was added slowly via syringe pump.^{11c} Indeed, with an aldehyde addition time of five hours, **5a** was isolated in 81% yield. Interestingly, an otherwise identical experiment conducted in the absence of benzoic acid resulted in an improved yield of 96%. Apparently, β -naphthol is sufficiently acidic to promote the required redox isomerization.

A number of experiments were performed in an effort to extend the α -arylation procedure to indole as the nucleophile (Table 1). In the absence of any additive, the reaction provided the undesired regioisomer **2b** as the major product (entry 1). The situation improved dramatically upon addition of 20 mol % of benzoic acid (entry 2). In the event, **5b/2b** were isolated in a 9.5:1 ratio and 79% combined yield. Carboxylic acids with slightly reduced acidities such as (4-dimethylamino)benzoic acid and 2-ethylhexanoic acid (2-EHA) provided slightly improved results (entries 3–4). Increasing the amount of 2-EHA to one equivalent led to an almost complete suppression of the undesired regioisomer and a further increase in the yield of **5b** (entry 6). Direct mixing of all components also resulted in an excellent product ratio but lower overall yield compared to the slow addition approach (entry 7).

In order to establish the impact of the aldehyde on product ratios, the reactions of pyrrolidine with either β -naphthol or indole were evaluated with two representative aldehydes, benzaldehyde and mesitaldehyde (eqs 2–3). Consistent with our observations in the α -alkynylation,^{4g} benzaldehyde gave relatively poor product ratios while mesitaldehyde provided the desired regioisomers with excellent selectivities.

(2)

(3)

The α -arylation procedure was applicable to various naphthols, phenols, indoles and pyrroles (Scheme 3). Excellent product ratios were obtained in most instances, including with phenols and pyrroles. Notably, these substrates provided poor results in the

corresponding decarboxylative three-component reaction that was developed previously by our group.^{11c} Piperidine also furnished the corresponding products with excellent regioselectivities, albeit in reduced yields.

In summary, we have developed unprecedented redox-neutral α -arylations of simple cyclic amines that are applicable to a range of naphthols, phenols, indoles and pyrroles. Further applications of our concept for redox-neutral amine α -functionalization are under development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Concept for redox-neutral amine α -functionalization.

Initial observation **Improved results** **Scheme 2.**

Initial results and optimized conditions for the α-arylation of pyrrolidine with β-naphthol.

Scheme 3.

Substrate scope for the α -arylation^a

^a Reactions were performed on a 1 mmol scale. Yields correspond to the desired regioisomers. ^b Reactions with β -naphthols and indoles: Ar'H (1.5 equiv); reactions with phenols or pyrroles: Ar'H (5 equiv); reactions with indoles and pyrroles: 2-EHA (1 equiv). ^c 2.5 equiv of 2-EHA were used. ^d 2,5-Disubstituted pyrrole product was isolated as a byproduct in 19% yield (dr = 3:1).

Table 1Evaluation of reaction conditions for the α -arylation of pyrrolidine with indole^a

(1)

entry	additive (mol %)	ratio 5b:2b	yield 5b+2b (%)
1	—	1:1.8	76
2	PhCOOH (20)	9.5:1	79
3	4-Dimethylamino benzoic acid (20)	11.3:1	81
4	2-Ethylhexanoic acid (20)	11.6:1	80
5	2-Ethylhexanoic acid (50)	21:1	85
6	2-Ethylhexanoic acid (100)	> 25:1	86
7 ^b	2-Ethylhexanoic acid (100)	> 25:1	71

^aReactions were performed on a 0.5 mmol scale.^bAll reagents were mixed directly and heated in toluene (0.25 M) under reflux for 15 min.