Published in final edited form as:

Org Lett. 2019 March 15; 21(6): 1845–1848. doi:10.1021/acs.orglett.9b00438.

Redox-Annulations of Cyclic Amines with Electron-Deficient *o*-Tolualdehydes

Anirudra Paul[†], Alafate Adili[†], and Daniel Seidel^{*}

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611, United States

Graphical Abstract:

Amines such as 1,2,3,4-tetrahydroisoquinoline undergo redox-neutral annulations with 2-methyl-3,5-dinitrobenzaldehyde and closely related substrates. Acetic acid serves as the solvent and sole promoter of these transformations which involve dual C–H functionalization.

Among methods that enable the α -C–H bond functionalization of amines,¹ redox-annulations of cyclic amines hold a unique place as they incorporate the concurrent functionalization of the amine nitrogen atom via C–N bond formation (Scheme 1).^{2–6} Thus, redox-annulations rapidly generate polycyclic amines from simple building blocks, only requiring carboxylic acids (typically AcOH or BzOH) as catalysts or promoters. *Ortho*-substituted benzaldehydes **1** are common substrates for redox-annulations, forming products **2** via C–N and concurrent α -C–X or α -C–C bond formation (eq 1). In the case of α -C–C bond formation, the presence of electron-withdrawing groups on the *ortho*-substituent appears to be required. For instance, simple *o*-tolualdehyde is insufficiently activated and fails to undergo annulation. Recently, the Wang group^{3c,3d} and we^{2j} independently found that 2-alkylquinoline-3-carbaldehydes (e.g., **3**) and related pyridine derivatives are sufficiently reactive to allow for the formation of products such as **4** via redox-annulation (eq. 2). We were curious to learn whether electron-deficient *o*-tolualdehydes **5** would also be amenable to annulation, generating products **6** containing the core structure of the tetrahydropyprotoberberine family of natural products (eq 3).⁷ Here we report the first examples of such a reaction.

The electron-deficient 2-methyl-3,5-dinitrobenzaldehyde (**5a**) was selected as a starting point to evaluate the proposed redox-annulation process, utilizing 1,2,3,4-tetrahydroisoquinoline (THIQ) as the model amine (Table 1).⁸ Under the optimized

^{*}Corresponding Author seidel@chem.ufl.edu.

[†]These authors contributed equally to this work.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data including the X-ray crystal structure of product **6b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

conditions (entry 1), product **6a** was obtained in 81% yield upon heating of **5a** (0.1 M concentration) with two equiv of THIQ in acetic acid solvent for a period of 2 h. A range of other conditions provided product **6a** in variable albeit lower yields. For instance, a reduction in the amount of acid (by using toluene as a cosolvent) was detrimental, as was a reduction in the amount of THIQ (entries 2–6). Slow addition of aldehyde **5a**, a strategy sometimes useful for improving the yields of certain redox-annulations, was not advantageous (entry 7). A reaction performed at a reduced temperature of 80 °C did not result in the formation of any detectable amounts of **6a** after 12 h (entry 8).

The scope of the amine redox-annulation with 2-methyl-3,5-dinitrobenzaldehyde (**5a**) is outlined in Scheme 2. A range of THIQ's with various substituents on the benzene ring readily underwent annulation to provide products **6** in moderate to good yields. 1-Aryl-THIQ's engaged **5a** to form tetrahydropyridoberberines **6** containing a tetrasubstituted stereogenic center. Both electron-donating and electron-withdrawing substituents on the aryl-group were tolerated. A reaction of 1-phenyl-1,2,3,4-tetrahydro- β -carboline with **5a** resulted in the formation of product **6o** in 54% yield. In regard to modifying the aldehyde starting material **5**, introduction of a chlorine or bromine substituent in the *para*-position of the formyl group was tolerated, enabling the preparation of products **6p–s**. Other modifications of the aldehyde **5** (e.g., removal of one of the nitro groups, replacement of one of the nitro groups with a different electron-withdrawing group, or change of the methyl group to ethyl) resulted in substrates that failed to undergo redox-annulations with THIQ under a variety of conditions, including microwave heating at 200 °C for a period of 15 min.

In summary, we have achieved redox-annulations of THIQ and substituted analogs with 2-methyl-3,5-dinitrobenzaldehyde (**5a**). These reactions provide rapid access to new tetrahydropyridoberberines.

ACKNOWLEDGMENT

Financial support from the NIH–NIGMS (Grant R01GM101389) is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for X-ray crystallographic analysis.

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Redox-annulation of amines with *ortho*-substituted benzaldehydes: **Redox-annulation with 2-alkylquinoline-3-carbaldehydes:** **Redox-annulation with electron-deficient *ortho*-tolualdehydes (this work):**

Scheme 1.
Selected Redox-Annulations of Amines

Scheme 2.
Scope of the Redox-Annulation

Table 1.

Reaction Development^a

entry	deviation from optimized conditions	time (h)	yield (%)
1	none	2	81
2	1 equiv of AcOH in PhMe (0.1 M)	6	38
3	20 equiv of AcOH in PhMe (0.1 M)	6	46
4	PhMe/AcOH = 1:1 (0.1 M)	2	69
5	1.3 equiv of THIQ	2	41
6	1.2 equiv of BzOH in PhMe (0.1 M)	2	36
7	slow addition of 5a over 15 h	15	75
8	reaction performed at 80 °C	12	-

^a All yields correspond to isolated yields of chromatographically purified product.