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The Rügheimer–Burrows reaction revisited: facile preparation of 4-alkylisoquinolines and 3,5-dialkylpyridines from (partially) saturated amines

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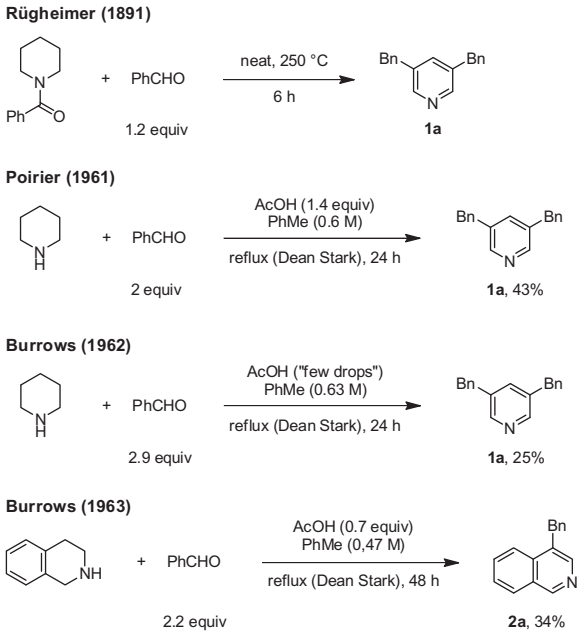
ABSTRACT

A long-known class of cyclic amine/aldehyde condensation reactions was reinvestigated. Benzoic acid was found to efficiently promote condensations of amines such as piperidine or 1,2,3,4-tetrahydroisoquinoline with aromatic aldehydes, resulting in amine β-functionalization and aromatization. These redox-neutral transformations provide 3,5-dialkylpyridines and 4-alkylisoquinolines in moderate to good yields, following short reaction times under microwave conditions.

Among the manifold methods for the C–H functionalization of amines, redox-neutral variants are particularly desirable as they eliminate the need for external oxidants.[1,2] Known for some time, largely due to the pioneering efforts of Grigg et al.,[3] is a class of reactions in which a secondary amine, upon condensation with an aldehyde, undergoes α-C—H bond functionalization with concurrent formation of an azomethine ylide.[4] While this type of reactivity has historically been limited to relatively activated amines (e.g., α-amino esters or amines with benzylic α-C—H bonds), it has recently been expanded to less reactive substrates.[5] The pericyclic chemistry of azomethine ylides, generated via amine/aldehyde condensations or otherwise, has been well studied, in particular in regard to [3+2]-cycloadditions.[4] Our group has developed a range of transformations in which an initial condensation of a secondary amine with an aldehyde or a ketone, via the intermediacy of an azomethine ylide, ultimately leads to amine α-functionalization,[6] α,α-difunctionalization,[7] or α,β-difunctionalization.[8,9] In these reactions, azomethine ylides do not engage in pericyclic reaction pathways, but rather serve as precursors to iminium ions or enamines that undergo a range of transformations. These reactions are well preceded by various amine/aldehyde condensation processes that lead to substrate aromatization.[10–14] In fact, such processes are likely the earliest examples of reactions that involve azomethine ylides. As a rapid entry to 3,5-dialkylpyridines and 4-alkylisoquinolines, here we report a reevaluation of what others have dubbed the Rügheimer–Burrows reaction.[11e]

The possibly earliest example of an amine aromatization process was described by Rügheimer in 1891 (Scheme 1).[10a,b] He discovered that heating of a neat mixture of *N*-benzoyl piperidine



Scheme 1. Examples of amine aromatization.

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and benzaldehyde to 250 °C results in the formation of 3,5-dibenzylpyridine. Some ambiguity exists as to the yield of this process. About 70 years later, following up on a 1958 study by Parker and Furst who noted the formation of unidentified products in piperidinium acetate catalyzed aldehyde condensation reactions,[15] a related transformation was investigated independently by the groups of Poirier[10c] and Burrows.[10d] These researchers found that condensations of piperidine with benzaldehyde, in the presence of acetic acid, provide varying amounts of **1a**. The original Rügheimer process was reevaluated by Poirier et al.,[10c] who found the need for harsher conditions in order to achieve efficient product formation (300 °C, 12 h, 54% yield of **1a**; 1:2 ratio of *N*-benzoyl piperidine and benzaldehyde). Burrows et al. concluded that the Rügheimer process most likely proceeds via the initial hydrolysis of *N*-benzoyl piperidine, with piperidine being the actual reactant.[10e] Burrows and coworkers also extended the scope of this transformation to 1,2,3,4-tetrahydroisoquinoline (THIQ) as a means to prepare 4-benzylisoquinoline (**2a**).[10e] This process was later improved and studied in detail by Dannhardt et al.,[11c–e] who provided conclusive evidence for the intermediacy of enamines and other proposed intermediates. The maximum yield thus far reported for **2a** is 59%. A number of related amine aromatization reactions were disclosed in more recent times. The Oda group reported the synthesis of 1,3-dialkylpyrroles from pyrrolidine and aldehydes.[13a] Interestingly, no carboxylic acids were employed in this process. Tunge et al. developed a strategy for the benzoic acid catalyzed synthesis of *N*-alkyl pyrroles from 3-pyrroline and aldehydes or ketones.[12c] Pan et al.[14a] and our group[14b] independently extended this strategy to the synthesis of *N*-alkyl indoles from indoline. We provided experimental evidence for the intermediacy of azomethine ylides in the corresponding reactions involving 3-pyrroline and indoline.[14b] Finally, the Yu group conducted a computational investigation of Tunge's pyrrole formation, providing interesting mechanistic proposals while lending further support to the notion that azomethine ylides play a role in these reactions.[12d]

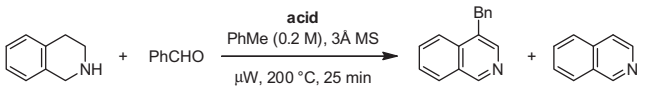
We set out to find operationally convenient conditions for the Rügheimer–Burrows reaction, using THIQ and benzaldehyde as the model substrates (Table 1). Because our primary interest was in achieving high yields in combination with brief reaction times, experiments were conducted under microwave conditions at elevated temperatures. In the absence of any carboxylic acid, no formation of **2a** was observed for a reaction conducted for 25 min at 200 °C in toluene (Table 1, entry 1). Instead, isoquinoline (**3**) was formed in 23% yield. Dannhardt had previously noted the formation of isoquinoline as an undesired byproduct.[11e] Disappointingly, addition of acetic acid (1.5 equiv) under otherwise identical conditions led to the isolation of **2a** in only 26% yield (Table 1, entry 2). Substantially higher yields were obtained when 2-ethylhexanoic acid (2-EHA) or benzoic acid was used as promoter (Table 1, entries 3 and 4). All three carboxylic acids were then tested at various loadings, with five equivalents of benzoic acid providing the best results (Table 1, entry 7). In the event, **2a** was isolated in 73% yield. Evaluation of other reaction parameters (solvent, temperature, etc.) did not lead to any further improvements. Reduced yields were also observed in the absence of molecular sieves while virtually identical results were obtained with 4 Å molecular sieves.

With favorable reaction conditions in hand, the scope of the 3-alkylisoquinoline formation was evaluated (Table 2). Aromatic aldehydes with electronically diverse substituents in different ring positions readily participated in reactions with THIQ. The resulting isoquinolines were isolated in moderate to good yields. Attempts to expand the substrate scope to enolizable aldehydes have thus far failed to provide the corresponding isoquinoline products.

Gratifyingly, nearly identical reaction conditions were applicable to the corresponding formation of 3,5-dialkylpyridines from piperidine and aldehydes (Table 3). Because of the incorporation of another alkyl substituent and the requirement for a minimum of three equivalents of aldehyde (see proposed mechanism), 3.3 equiv of aldehyde were employed. Yields were excellent in some cases and generally higher than those of the corresponding isoquinolines.

The substrate scope was further extended to the formation of a quinoline. Burrows et al. had reported that reactions of 1,2,3,4-tetrahydroquinoline (THQ) fail to provide the expected 3-benzylquinoline products because THQ engages in Friedel–Crafts-type reactions at the 6-position of this anilinic heterocycle.[10e] Using 6-chloro-THQ and benzaldehyde, these authors succeeded in the preparation of the corresponding quinoline in 20% yield. We evaluated the analogous and readily available 6-bromo-THQ[16] in a reaction with benzaldehyde (Scheme 2). Perhaps not surprisingly, higher reaction temperatures were required. Nevertheless, product **4** was isolated in 60% yield; 6-bromoquinoline was observed as a byproduct.

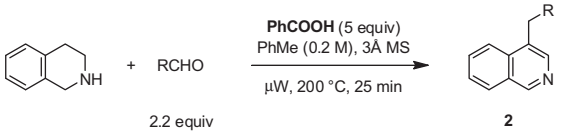
Table 1
Evaluation of reaction conditions[a]



Entry	Acid (equiv)	Yield of **2a** (%)	Yield of **3** (%)
1	None	—	23
2	AcOH (1.5)	26	9
3	2-EHA (1.5)	45	18
4	$PhCO_2H$ (1.5)	54	7
5	AcOH (5)	32	16
6	2-EHA (5)	59	9
7	$PhCO_2H$ (5)	73	6
8	AcOH (10)	63	8
9	2-EHA (10)	52	22
10	$PhCO_2H$ (10)	71	6
11	$PhCO_2H$ (3)	64	6

[a] Reactions were performed on a 0.2 mmol scale.

Table 2
Scope of the isoquinoline formation[a]



Entry	R	Product	Yield (%)
1	C_6H_5	**2a**	73
2	4-Me–C_6H_4	**2b**	76
3	4-MeO–C_6H_4	**2c**	70
4	4-F–C_6H_4	**2d**	68
5	4-Cl–C_6H_4	**2e**	67
6	4-Br–C_6H_4	**2f**	62
7	4-NO_2–C_6H_4	**2g**	56
8	3-MeO–C_6H_4	**2h**	72
9	3-Br–C_6H_4	**2i**	65
10	2-MeO–C_6H_4	**2j**	71
11	2-Br–C_6H_4	**2k**	62
12	4-Pyridyl	**2l**	54
13	2-Naphthyl	**2m**	68

[a] Reactions were performed on a 0.2 mmol scale.