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Ring-fused aminals: catalyst and solvent-free microwave-assisted α-amination of nitrogen heterocycles

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ABSTRACT

A high-yield synthesis of ring-fused aminals via microwave (MW)-assisted α-amination of nitrogen heterocycles at 130 °C under solvent- and catalyst-free conditions is described.

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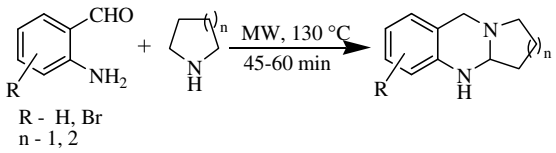
1. Introduction

Ring-fused aminals, found in number of natural products,[1] are of considerable interest as useful building blocks and as potential drug candidates.[2] Direct functionalization of heterocycles is one of the best and shortest routes to these aminals, which otherwise need multi-step synthesis.[3,4] Recently, Seidel et al. pioneered a new α-amination protocol of cyclic amines that provides one-pot synthesis of ring-fused aminals of nitrogen heterocycles.[5] However, this novel method needs as much as 80 h for completion of the reaction. In light of this, an expedient and simple version of this protocol is highly desirable.

The nonclassical MW heating technique termed as the 'Bunsen burner of the 21st century' is rapidly becoming popular, and the use of emerging MW-assisted chemistry techniques is dramatically reducing chemical waste and reaction times in several organic syntheses and chemical transformations.[6] Consequently, we decided to explore this technique for Seidel's sluggish α-amination protocol.

Engaged in the development of greener synthetic pathways,[6,7] herein, we report an expeditious and eco-friendly synthesis of ring-fused aminals under MW irradiation conditions without using any catalyst or solvent (Scheme 1).



Scheme 1. MW-assisted synthesis of ring-fused aminals.

Initially, the α-amination reaction of pyrrolidine with 2-amino benzaldehyde under MW irradiation was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Table 1).

First, the reaction was conducted as per Seidel's conditions[5] using ethanol as a solvent at 130 °C for 30 min under MW irradiation conditions, and a moderate 30% conversion was observed (Table 1, entry 1). As the reaction time was increased up to 1 h, a good conversion (65%) was achieved (Table 1, entry 2). With a view to

Table 1
Optimization of reaction conditions

Entry	Solvent	Temperature (°C)	Reaction time (min)	Conversion (%)
1	Ethanol	130	30	30
2	Ethanol	130	60	65
3	No solvent	130	30	50
4	No solvent	130	45	75
5	No solvent	130	60	79

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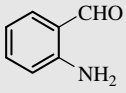
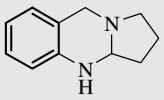
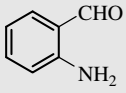
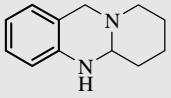
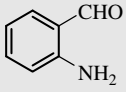
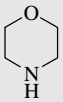
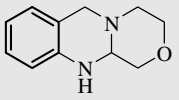
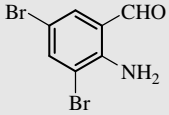
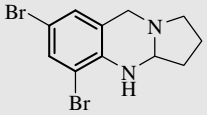
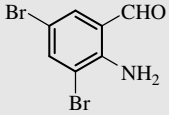
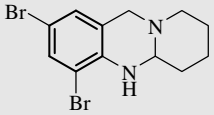
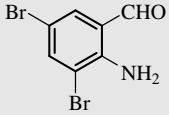
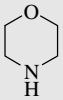
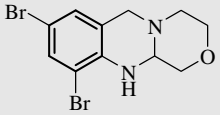
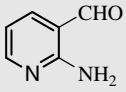
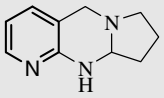
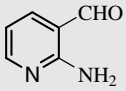
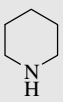
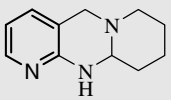
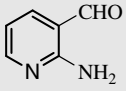
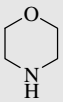
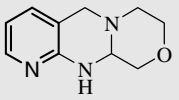
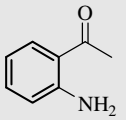
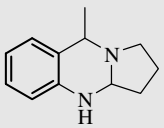
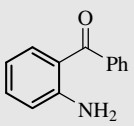
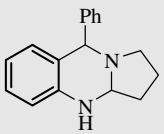
develop a relatively benign protocol, we carried out the reaction under solvent-free conditions at 130 °C for 30 min, when moderate conversion (50%) was achieved, and this was further improved to 75% by increasing the reaction time to 45 min (Table 1, entries 3 and 4). Further increase in reaction time did not improve the final conversion (Table 1, entry 5).

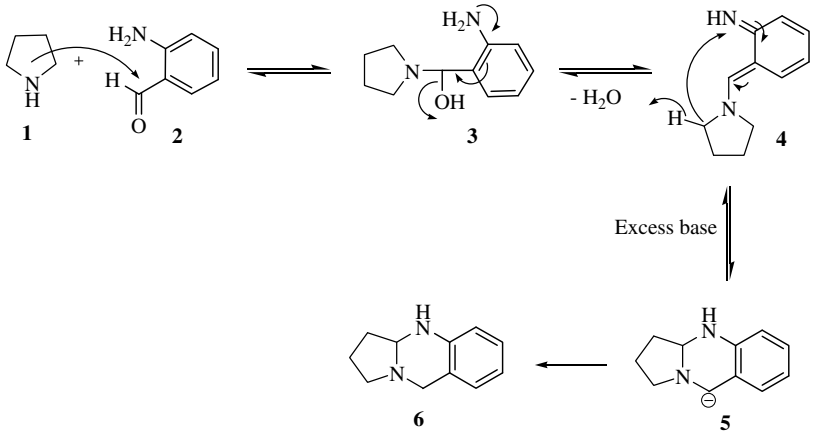
With the above optimized reaction conditions, α-amination reactions of a series of cyclic amines with amino benzaldehydes were probed under solvent- and catalyst-free conditions. A variety of substrates were successfully reacted to form respective ring-fused aminals with good yields (Table 2).

Excellent conversions were observed for various aminoaldehydes and cyclic amines within 1–2 h. Unsubstituted as well as substituted aminoaldehydes underwent α-amination reaction under solvent-free and catalyst-free conditions with good yield, proving the general applicability of this protocol for expeditious

Table 2
MW-assisted α-amination reaction under solvent- and catalyst-free conditions[a]

Entry	Aminoaldehyde	Cyclic amines	Product	Reaction time (min)	Yield[a] (%)
1				60	75
2				60	65
3				60	64
4				45	82
5				45	62
6				45	65
7				60	15
8				60	12
9				60	10
10				60	45
11				60	NR

[a] GC yield.



Scheme 2. Mechanism of the synthesis of ring-fused aminals.

assembly of a variety of heterocycles. Compared to unsubstituted substrates (Table 2, entry 1), dibromo-substituted aminoaldehydes (Table 2, entry 4) gave higher product yield in a shorter reaction time. This maybe due to activation of aminoaldehyde group by two bromine groups. In the case of 2-aminopyridine-3-carbaldehyde, although the reactions proceeded smoothly, the decrease in yield is due to instability of these substrates under MW-conditions (Table 2, entries 7–9). We also attempted the α-amination using amino ketones, and did succeed in formation of the respective ring-fused aminal, 1-(2-aminophenyl)ethanone (Table 2, entry 10), with 45% yield. However, no reaction was observed for the aromatic analogue, (2-aminophenyl)(phenyl)methanone (Table 2, entry 11). The formation of transesterification by-products, which was an issue with Seidel's α-amination protocol,[5] was not observed, as the entire process was under solvent-free condition.

This reaction closely resembles Friedlander's protocol for quinoline synthesis.[8–11] The general mechanism of the Friedländer synthesis is well understood,[12,13] and recently Muchowski and Maddox have commented on it.[14] On this basis, we hypothesize the following mechanism for this MW-assisted synthesis of ring-fused aminals (Scheme 2).

The first step is the addition of cyclic amine to aldehyde carbonyl group to form intermediate **3**, which is followed by dehydration (MW-assisted) to form dienimine-type intermediate **4**. The deprotonation of α-H of pyrrolidine ring in intermediate **4** by excessive cyclic amines, followed by cyclization forms intermediate **5**, which on protonation delivers the final ring-fused aminals **6**.

In conclusion, we have developed a rapid and sustainable protocol for α-amination of cyclic amines with variety of aminoaldehydes which proceeds exclusively without any catalyst or solvents under MW irradiation conditions. It is remarkable that the solvent-free conditions do not prevent higher yield of the products. This reaction maybe very useful in drug discovery, and will avoid multi-step synthesis for ring-fused aminals.

2. Experimental

Typical experimental procedure for ring-fused aminal synthesis: The aminoaldehydes (1 mmol) and cyclic amines (4 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The sealed reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 130 ± 5 °C (temperature monitored by a built-in infrared sensor), power 10–200 W, and pressure 50–100 psi for required reaction time (Table 2). After completion of the reaction, crude products were purified by column chromatography. Spectral data of representative compounds are given below.

2.1. 5,7-Dibromo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-*b*]-quinazoline

^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 7.00 (s, 1H), 4.41 (m, 1H), 4.25 (s, 1H), 4.12 (d, 1H), 3.80 (d, 1H), 2.80 (m, 2H), 2.20 (m, 1H), 1.98 (m, 2H), 1.75 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.5, 32.5, 50.0, 70.9, 108.2, 109.1, 121.1, 128.6, 131.9, 139.5 ppm; MS: (M^+) 332.

2.2. 2,4-Dibromo-5a,6,7,8,9,11-hexahydro-5H-pyrido[2,1-*b*]-quinazoline

^{1}H NMR ($CDCl_3$): δ 7.50 (s, 1H), 6.98 (s, 1H), 4.23 (s, 1H), 3.82 (s, 1H), 3.78 (m, 2H), 2.98 (m, 1H), 2.24 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.65 (m, 2H), 1.60 (m, 1H), 1.48 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.1, 25.8, 32.0, 51.6, 56.1, 70.0, 108.2, 108.4, 121.9, 128.3, 131.9, 139.2 ppm; MS: (M^+) 346.

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