Rapid Microwave-Assisted Reductive Amination of Ketones with Anilines

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Abstract: Using microwave technology, a new protocol has been developed that improves the reaction rate and overall efficiency of the direct reductive amination of ketones with anilines. When using sodium triacetoxyborohydride as the reducing agent, high product yields and increased reaction rates are achieved for a variety of electronically different anilines. Furthermore, we have found that this protocol can also be applied to aldehydes.

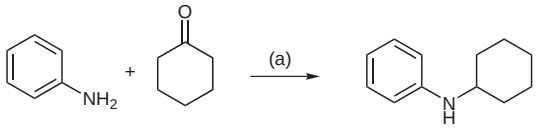
Key words: reductive amination, anilines, ketones, microwave synthesis, aldehydes

The synthesis of secondary and tertiary amines by the reductive amination of carbonyl compounds is a versatile and widely used transformation available to the modern synthetic chemist. Additionally as aromatic amines are present in a large number of marketed pharmaceuticals it is not surprising that a variety of protocols have been reported in the chemical literature.[1,2] These methods can usually be categorised into two distinct areas. The first is an indirect/stepwise method where the intermediate imine is pre-formed and then reduced in an independent step.[1] The second are direct reductive amination methods that are much more convenient as prior formation of the imine is not necessary; the carbonyl compound, the amine and the reducing agent are all present at the outset of the reaction.[3] Traditionally, sodium cyanoborohydride has been the reducing agent of choice in these direct reactions.[4] However, the reagent and its by-products are highly toxic, which is undesirable. Sodium triacetoxyborohydride has been identified as a mild and efficient alternative,[5] which exhibits good selectivity and will reduce aldehydes preferentially over ketones. Moreover, imines are much more basic than their carbonyl counterparts and thus are preferentially reduced by sodium triacetoxyborohydride.

Sodium triacetoxyborohydride has been utilised successfully for the reductive amination of a wide variety of ketones with differing primary and secondary amines.[6] However, when anilines are used more extensive reaction times are necessary.[7] Anilines are weakly basic amines (p*K*a ~ 4.6,[8] compare with 10.7 for cyclohexylamine[9]) due mainly to the partial delocalisation of the nitrogen lone pair into the aromatic benzene ring.[10] Anilines are much less nucleophilic than aliphatic amines and, as a consequence, longer reaction times are needed. Indeed, because of this Abdel-Magid's group demonstrated the use of several different sets of reaction conditions for the direct reductive amination of anilines.[6a–6c] Therefore, we felt that a more general, user-friendly protocol that would allow for the rapid synthesis of aromatic amines would be extremely beneficial. Additionally, we were intrigued as to whether the use of modern microwave technology could enhance the reaction rate and overall efficiency of the reductive amination process.[11,12] Herein, we present our initial findings in this area.

At the outset of this study, and in order to optimise a microwave-assisted direct reductive amination process, the general method described by Abdel-Magid and co-workers was used as a basis.[6a–6c] In this regard, a standard reaction between aniline and cyclohexanone was selected to carry out an initial time and temperature study. The reaction was carried out in sealed microwave tubes containing a solution of aniline, cyclohexanone (2 equiv), sodium triacetoxyborohydride (2.5 equiv) and acetic acid (3 equiv) in toluene which was then heated for various times and temperatures using a CEM Discover® instrument (Table 1).[13] It was found that a successful reaction could be achieved at 100 °C in only ten minutes (entry 1). Moreover, it was discovered that the yields of desired product could be enhanced to 87% by increasing the temperature to 140 °C (entry 3). Interestingly, heating beyond this temperature proved to be detrimental to the product yields

Table 1 The Effects of Time and Temperature on the Reductive Amination of Cyclohexanone with Aniline[a]



Entry	Time (min)	Temp (°C)	Yield (%)[b]
1	10	100	70
2	10	120	81
3	10	140	87
4	10	160	81
5	10	180	77
6	15	120	84
7	15	140	86

[a] Reaction conditions: aniline (1 mmol), cyclohexanone (2 mmol), $NaBH(OAc)_3$ (2.5 mmol) and AcOH (3 mmol) in toluene (2 mL) were heated in a CEM Discover® instrument.
[b] Yield of isolated product.

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(entries 4 and 5). Furthermore, a ten-minute reaction time seemed to be optimal, as heating for a longer time period showed no significant benefits (entries 6 and 7).

In order to further optimise the reductive amination process we felt that it was crucial to investigate an array of solvents that possessed different microwave properties (Table 2).[11,14] Whilst all solvents performed very well, the yield of 94% that was obtained with 1,2-dichloroethane (DCE) was particularly impressive (entry 2). Therefore, all further reactions were carried out using DCE as the solvent. Nevertheless, the result of 91% obtained with acetonitrile (entry 4) is comparable and, if required, this could be used as an alternative.

Table 2 The Effects of Solvents Used in Reductive Amination of Cyclohexanone with Aniline[a]

Entry	Solvent	Yield (%)[b]
1	Toluene	87
2	THF	79
3	DCM	81
4	Acetonitrile	91
5	1,2-DCE	94

[a] Reaction conditions: aniline (1 mmol), cyclohexanone (2 mmol), $NaBH(OAc)_3$ (2.5 mmol) and AcOH (3 mmol) in the stated solvent (2 mL) were heated in a CEM Discover® instrument at 140 °C for ten minutes.
[b] Yield of isolated product.

Next we examined whether the reducing agent and/or the acid could be substituted for alternative reagents (Table 3). First, it was found that both sodium cyanoborohydride and resin-bound sodium triacetoxyborohydride[15] resulted in inferior yields (entries 1 and 2). Second, the role of the acetic acid is clearly very important,[16] as attempts to substitute this for other acidic derivatives resulted in lower yields (entries 3–5). However, the yield of ~70% obtained with the use of the reducing agent MP-sodium triacetoxyborohydride is still synthetically useful

Table 3 Alternative Reagents for the Reductive Amination of Cyclohexanone with Aniline[a]

Entry	Acid	Reductant	Yield (%)[b]
1	AcOH	$NaCNBH_4$	56
2	AcOH	MP-$BH(OAc)_3$[c]	69
3	TsOH	$NaBH(OAc)_3$	45
4	Amberlite IRC50-H	$NaBH(OAc)_3$	64
5	MP-TsOH[c]	$NaBH(OAc)_3$	35

[a] Reaction conditions: aniline (1 mmol), cyclohexanone (2 mmol), reducing agent (2.5 mmol) and acid (3 mmol) in DCE (2 mL), were heated in a CEM Discover® instrument at 140 °C for ten minutes.
[b] Yield of isolated product.
[c] MP = macroporons polystyrene.

(entry 2). In addition, this reagent does offer the benefit of a simple filtration rather than an aqueous work-up to obtain the product.

Now that optimised microwave conditions had been established, reductive aminations were attempted with a range of electronically different anilines and ketones of varying reactivity (Table 4).[17] Cyclopentanone and hexan-2-one reacted extremely readily with aniline to provide excellent yields of 88% and 92%, respectively (entries 2 and 3). Even the much less reactive cyclooctanone provided a good yield of 68% in only ten minutes (entry 4). In almost every instance the use of microwave irradiation to facilitate the reductive amination of various anilines was highly successful, with reactions reaching completion in just ten minutes. Moreover, both *p*-methoxyaniline and *o*-toluidine reacted extremely well with a variety of ketones (entries 5–11). However, and perhaps not surprisingly, reactions involving the electron-deficient anilines, *o*-bromoaniline and *p*-nitroaniline, gave moderate yields (entries 12–15). It should be noted that in these cases it was still possible to observe some of the starting aniline by TLC.[18] Nevertheless, this protocol still allowed for the swift formation of synthetically very useful building blocks.

Table 4 Microwave-Assisted Reductive Amination between Anilines and Ketones[a]

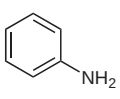
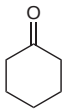
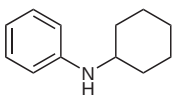
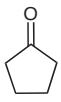
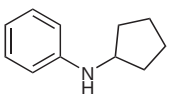
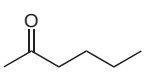
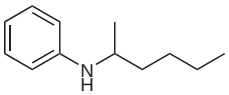
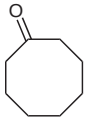
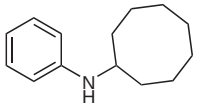
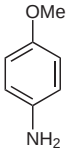
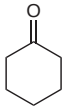
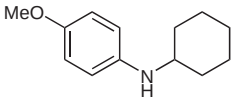
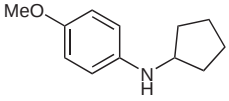
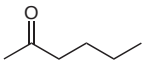
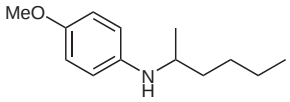
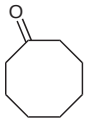
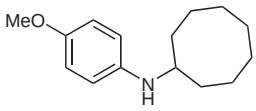
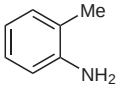
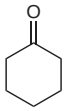
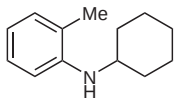
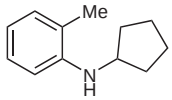
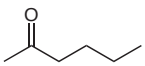
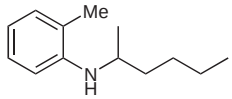
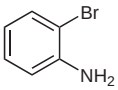
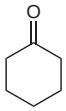
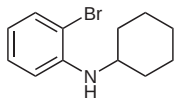
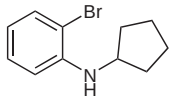
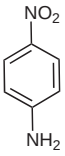
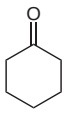
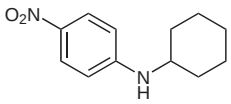
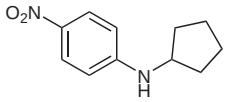
Entry	Aniline	Ketone	Product	Yield (%)[b]
1				94[19]
2				88[19]
3				92[19]

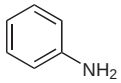
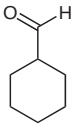
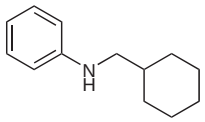
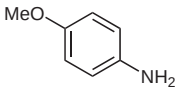
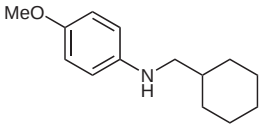
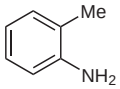
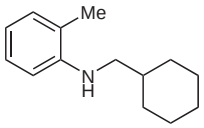
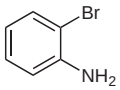
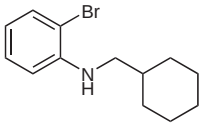
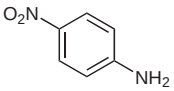
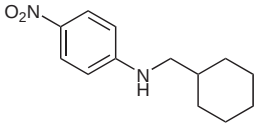
Table 4 Microwave-Assisted Reductive Amination between Anilines and Ketones[a] (continued)

Entry	Aniline	Ketone	Product	Yield (%)[b]
4				68[20]
5				77[19]
6				64[19]
7				87[20]
8				64[20]
9				95[19]
10				81[19]
11				92[20]
12				56[19]
13				40[20]
14				34[19]
15				26[20]

[a] Reaction conditions: Aniline (1 mmol), ketone (2 mmol), $NaBH(OAc)_3$ (2.5 mmol) and AcOH (3 mmol) in DCE (2 mL) were heated in a CEM Discover® instrument at 140 °C for ten minutes.
[b] Yield of isolated product.

To explore the scope of these newly developed reductive amination conditions, the reaction between various anilines and an aldehyde, cyclohexanecarbaldehyde, was examined (Table 5).[21] However, due to the increased reactivity of aldehydes, when using our standard protocol the di-alkylated compound was found to be the major prod-

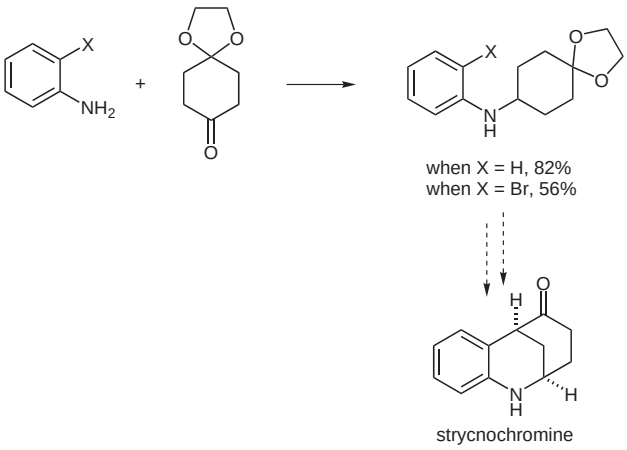
Table 5 Microwave-Assisted Reductive Amination between Anilines and Aldehydes[a]

Entry	Aniline	Aldehyde	Product	Yield (%)[b]
1				91[19]
2				83[19]
3				88[19]
4				75[19]
5				61[19]

[a] Reaction conditions: Aniline (2 mmol), aldehyde (1 mmol), $NaBH(OAc)_3$ (2.5 mmol) and AcOH (3 mmol) in DCE (2 mL) were heated in a CEM Discover® instrument at 140 °C for ten minutes.
[b] Yield of isolated product.

uct. This problem was overcome by utilising the aldehyde as the limiting reagent. Indeed, the desired mono-alkylated products were then obtained successfully in excellent yields of up to 91%. Even the very unreactive *o*-bromoaniline and *p*-nitroaniline provided the desired products in very good yields of 75% and 61%, respectively (entries 4 and 5).

Having established that our newly developed microwave protocol enhances the direct reductive amination of a good range of substrates, we were keen to demonstrate the mildness of this technique. To this end, 1,4-cyclohexanedione monoethylene acetal, containing an acid-labile acetal protecting group, was chosen to undergo reductive amination with aniline and *o*-bromoaniline (Scheme 1). Using our general protocol, the reaction proceeded efficiently to give the desired products in good yields of ~80% and 60%, respectively. Interestingly, Solé et al. required a reaction time of three days to achieve similar yields for this transformation with *o*-bromoaniline.[22] Importantly, from this aryl bromide intermediate, Solé et al. quickly and elegantly access very interesting bridged intermediates that have been used in the synthesis of two members of the *Strychnos* alkaloid family, the insecticide Aspernomine[23] and the anti-malarial Strycnochromine (Scheme 1).[24] The intermediate has three points where functionalisation is facile and this allows for rapid diversification of the scaffold. Therefore, we feel that the use of our protocol allows for an even more efficient approach to templates of extreme biological interest.



Scheme 1 Microwave-assisted reductive amination with an acid-sensitive substrate. *Reagents and conditions*: aniline (1 mmol), ketone (2 mmol), $NaBH(OAc)_3$ (2.5 mmol) and AcOH (3 mmol) in DCE (2 mL) were heated in a CEM Discover® instrument at 140 °C for ten minutes.

In summary, the microwave-assisted direct reductive amination procedure reported here offers many advantages over the more traditional methods. The most beneficial being the rapid reaction time, with the vast majority of reactions producing excellent yields after merely ten minutes. Additionally, as demonstrated above, the reaction conditions are mild and simple; sodium triacetoxyborohydride is much less toxic than the alternative sodium cyanoborohydride and an acid sensitive functionality is

tolerated by our system. A further advantage of this procedure is that inert atmospheric conditions are not necessary. This, coupled with only minimal work-up and straightforward flash column chromatography, means that the reactions are operationally very simple.

In conclusion, we have demonstrated that modern focused microwave reactors are readily utilisable and are reliable tools for the promotion of the direct reductive amination of both electron-rich and electron-poor anilines. The use of this technique results in the formation of functionalised anilines that are potentially very interesting scaffolds for the design of drug-like molecules. Indeed, this technique results in rapid and efficient access to a vast array of very interesting and versatile aromatic amines.

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(16) The acetic acid is believed to protonate the intermediate imine which assists in its reduction, see reference 6.

(17) Representative experimental procedure for the reductive amination of ketones: To a solution of aniline (100 mg, 1.07 mmol) and cyclohexanone (210 mg, 2.14 mmol) in DCE (2.1 mL) in a microwave vial, was added $NaBH(OAc)_3$ (567 mg, 2.68 mmol) and AcOH (193 mg, 3.21 mmol). The vial was capped and the resulting solution was heated in a CEM Discover® microwave for ten minutes (fixed hold time) at 140 °C. The reaction was quenched with $NaHCO_3$ (10 mL, sat. aq) and then extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (eluting with CH_2Cl_2) gave cyclohexylphenylamine as a viscous oil (177 mg, 94%).[19]

(18) It should be noted that in these cases the starting aniline was not isolated.

(19) All known compounds exhibited spectroscopic data consistent with that reported in the chemical literature.

(20) All new compounds exhibited the expected NMR, HPLC, LCMS and IR data which will be reported in a full publication in due course.

(21) Representative experimental procedure for the reductive amination of aldehydes: To a solution of aniline (200 mg, 2.2 mmol) and cyclohexanecarbaldehyde (123 mg, 1.1 mmol) in DCE (2.1 mL) in a microwave vial, was added $NaBH(OAc)_3$ (567 mg, 2.68 mmol) and AcOH (193 mg, 3.21 mmol). The reaction was then subjected to the same procedure described in reference 17. Purification gave cyclohexylmethylphenylamine as a viscous oil (185 mg, 91%).[19]

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