Tetrahedron Letters 51 (2010) 5210–5212

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-accelerated reductive amination between ketones and ammonium acetate

Li Dong *, Saadat Aleem, Cynthia A. Fink

Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540, USA

ARTICLE INFO

Article history:
Received 12 July 2010
Revised 26 July 2010
Accepted 27 July 2010
Available online 2 August 2010

ABSTRACT

A new procedure for reductive amination between ketones and ammonium acetate has been developed to access a variety of primary amines. This protocol takes advantage of microwave heating to significantly accelerate the reaction and offers a convenient and effective method to access some interesting amines. This new procedure compares favorably to previously reported approaches in terms of practicality, efficiency, and functional group compatibility.

1. Introduction

As part of our work to investigate the SAR of a lead series for a medicinal chemistry project, we required several racemic, conformationally restricted benzyl amine derivatives (Fig. 1). Since many of them were not commercially available, we needed to identify a general and efficient way to access these compounds. Although the synthesis of secondary and tertiary amines by reductive amination reactions of carbonyl compounds has been widely utilized, the preparation of primary amines using analogous methods is not as straightforward.[1] Previous reports indicate that there are two general approaches to synthesize these compounds using this methodology. In the first, a discrete intermediate imine or oxime is formed followed by a separate reduction step utilizing Pd/H_2, $LiAlH_4$, or Na.[2] Although this two-step approach generally affords a good yield of the desired product, there is the potential for functional group incompatibility due to the harsh reducing conditions. Alternatively, the direct reductive amination reactions of 1-indanone and 1-tetralone to access primary amines require either NH_3 and Raney Ni at high pressure[3] or a low-yielding condition of NH_4OAc and $NaCNBH_3$.[4] As none of these alternatives seemed attractive, we were determined to identify a more efficient and straightforward approach to prepare these useful structural motifs.

One objective of this research was to maintain many advantages of reductive amination reactions such as broad scope, versatility, and ease of operation. Toward this end, we first selected $NaCNBH_3$ as the reducing agent while deciding that NH_4OAc was a practical choice as the ammonia source. Early on, we were aware of the challenges of these conditions including low reactivity of aryl ketone substrates, instability of ammonium acetate under heat, and more importantly, the competing reaction involving the resulting primary amine and the starting ketone. We believed that a large excess of NH_4OAc would be necessary to suppress this side reaction.

In recent years, microwave-assisted reactions have gained increasing popularity due to their unique reaction profiles and impressive capability and versatility.[5] In fact, since the 1990s, scientists have used this new tool to improve yields, shorten reaction time, and achieve cleaner reductive amination reactions.[6] Due to the known pronounced acceleration achieved with microwave heating, we decided to use this method to promote our reactions.

2. Results and discussion

The initial screening of reaction conditions is summarized in Table 1. Reaction of 4-bromo-2,3-dihydro-1*H*-inden-1-one (**1**) with 15.0 equiv of NH_4OAc and 1.2 equiv of $NaCNBH_3$ in methanol at 90 °C for 2 min failed to give any significant quantities of the anticipated product, affording mostly recovered starting material. Increasing the reaction time to 5 min did not improve the conversion (entry 2). Using ethanol as the solvent allowed us to explore how higher temperatures would affect the reaction. At 130 °C, the reaction proceeded smoothly to give 76% yield of the desired amine in just 2 min. Encouraged by this result, a lower amount of NH_4OAc (10.0 equiv) as well as higher temperature and shorter reaction time was attempted. Unfortunately, reaction yields suffered in these cases (entries 4 and 5). It is also worth noting that in all examples, side product **3** was not detected by LC–MS in the crude mixture.

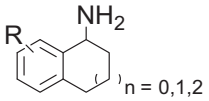
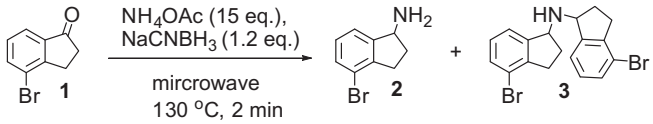


Figure 1.

* Corresponding author. Tel.: +1 908 740 4711; fax: +1 908 740 3705.
E-mail address: li.dong@spcorp.com (L. Dong).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.156

Table 1
Microwave-accelerated reductive amination of ketone **1** and ammonium acetate[a]

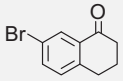
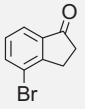
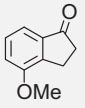
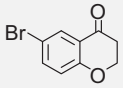
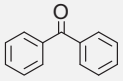
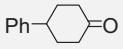
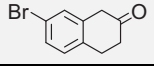


Entry	NH_4OAc (equiv)	Solvent	Temperature (°C)	Time (min)	Yield (**2**)[b] (%)
1	15.0	MeOH	90	2	<5
2	15.0	MeOH	90	5	<5
3	15.0	EtOH	130	2	76
4	10.0	EtOH	130	2	62
5	15.0	EtOH	160	1.5	40

[a] $NaCNBH_3$ (1.2 equiv), solvent (1.2 mL), ketone **1** (100 mg).
[b] Yield based on LC–MS for entries 1 and 2, isolated yields for entries 3–5 (purified by prep-HPLC).

Two more experiments were carried out before we decided the optimal conditions. First, the conventional thermal conditions were compared to microwave heating used in the above studies. When the reaction was heated in a sealed tube at 90 °C for 10 h, we received only 41% isolated yield of the desired product with complete consumption of ketone **1**. The major side product under this reaction condition was compound **3**. Furthermore, $Na(OAc)_3BH$ was used as the alternative reducing agent and surprisingly, this change caused a complete reversal of the reaction profile as only compound **3** was obtained in 72% yield using the otherwise same conditions.

Table 2
Reactions of various ketones

Entry	Substrate	Yield (%)
1		68
2		81
3		76
4		83
5		66
6		88
7		95
8		78
9		85
10		83
11		Complex mixture

With the optimized conditions in hand, we then investigated the substrate scope of this new protocol. We exposed a variety of ketones to the microwave-accelerated reductive amination conditions and the results are summarized in Table 2. In most cases, LC–MS analysis of the crude reaction mixtures indicated that the reactions proceeded cleanly. Reaction with acetophenone gave α-methyl benzylamine in modest yield, reflecting the difficulty in handling compounds of low molecular weight and good water solubility (entry 1). The reaction was tolerant of different ring sizes including 5-, 6-, and 7-membered rings, and also proceeded in the presence of steric hindrance flanking the aromatic ring (entries 2–4 and 6). However, electron-donating groups such as methoxy on the aromatic ring led to diminished yield of the desired product.[7] Heteroatoms were tolerated on the neighboring aromatic ring or as part of a ring containing the ketone (entries 7 and 8). Finally, both diaryl and alkyl ketones are suitable substrates for this methodology (entries 9 and 10). Unlike other examples, in the case of entry 10, a small amount (<10%) of bisalkylated product similar to **3** was also isolated. Not surprisingly, base-sensitive β-tetralone is not a suitable substrate for this reductive amination procedure as only an intractable mixture was obtained.

3. Conclusions

In conclusion, a convenient and efficient reductive amination protocol for the preparation of primary amines was developed utilizing microwave heating. A variety of ketones reacted with NH_4OAc and $NaCNBH_3$ under these conditions to afford the desired primary amine rapidly and in good yield. We believe that this improved procedure will be valuable in the preparation of many biologically interesting molecules containing primary amine functionalities.

4. Experimental

Ammonium acetate (513.5 mg, 6.66 mmol) and sodium cyanoborohydride (33.5 mg, 0.533 mmol) were added to a solution of 6-bromochroman-4-one (100 mg, 0.444 mmol) in EtOH (1 mL) in a 2 mL microwave vial. The mixture was stirred and heated at 130 °C for 2 min in a microwave reactor (Biotage Initiator®). The reaction mixture was concentrated to remove most of the EtOH, treated with 2 N NaOH until pH >10, and extracted with EtOAc (2×10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude product which was usually more than 90% pure (LC–MS). An analytical sample was obtained by prep HPLC as a formate salt. ^1H NMR (CD_3OD, 400 MHz, ppm): $\delta = 2.13$ (m, 1H), 2.35 (m, 1H), 4.31 (m, 2H), 4.56 (m, 1H), 6.87 (d, $J = 6.8$ Hz, 1H), 7.56 (dd, $J = 2.0$, 6.8 Hz, 1H), 7.62 (m, 1H), 8.62 (s, 1H).

Acknowledgment

We thank Dr. G. Greg Zipp for his generous assistance in preparation of this Letter.

References and notes

1. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
2. (a) Gutman, A. L.; Etinger, M.; Nisnevich, G.; Polyak, F. *Tetrahedron: Asymmetry* **1998**, *9*, 4369–4379; (b) Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* **1977**, *20*, 771–776; (c) Gomtsyan, A. R. U.S. Patent 200,82,87,676, 2008; (d) Herzig, Y.; Lerman, L.; Goldenberg, W.; Lerner, D.; Gottlieb, H. E.; Nudelman, A. *J. Org. Chem.* **2006**, *71*, 4130–4140; (e) Meng, Y.-Q.; Wang, Z.; Cheng, M.-S. *Zhonggui Xinyao Zazhi* **2003**, *12*, 457–458.
3. Gomtsyan, A. R.; Bayburt, E. K.; Lee, C.; Koenig, J. R.; Schmidt, R. G.; Lukin, K. A.; Chambournier, G.; Hsu, M. C.-P.; Leanna, R. M.; Cink, R. D. U.S. Patent 200,82,87,676, 2008.
4. Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849–2853.
5. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
6. (a) Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Dominguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, *37*, 8177–8180; (b) Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293–6298; (c) Bailey, H. V.; Heaton, W.; Vicker, N.; Potter, B. V. L. *Synlett* **2006**, 2444–2448; (d) Kangasmetsä, J.; Johnson, T. *Org. Lett.* **2005**, *7*, 5653–5655.
7. No starting material was isolated after the reaction. Unidentified side products were formed with this substrate.