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Reductive amidation of nitroarenes: a practical approach for the amidation of natural products

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ABSTRACT

A simple and practical approach for the one-pot conversion of nitroarenes into amide derivatives has been developed. Zinc and acetic acid are utilized as a reducing agent, and acyl chloride and triethylamine are used as the acylating agent in DMF with good yield (~60%) of the amide. This method was applicable to manzamine A (**1**), where the yield of 6-cyclohexamidemanzamine A (**7**) was significantly improved (56%) by this approach relative to (17%) by beginning with the amine.

Aryl amides are an important structural unit of many biologically important compounds as well as a number of drug candidates (Fig. 1).[1] Usually, the amides are obtained from the corresponding nitro intermediates in two separate steps: the reduction of the nitro group to the corresponding amine, followed by amidation with an activated carboxylic acid. The reduction of the nitro group to the corresponding amine can be completed using a number of approaches. Metal-catalyzed reductions are the most common in which a variety of metals have been reported including zinc,[2] iron,[3] platinum oxide,[4] palladium,[5] Raney nickel,[6] copper,[7] and ruthenium sulfide.[8]

Although the amine can be purified and subsequently reacted with an activated carboxylic acid the stability of some aromatic amines, especially the complex natural product derived amines, may affect the yield of the acylation reaction. Good examples of unstable amines are 6- and 8-aminomanzamine A (**5** and **6**). Manzamine A (**1**), the first representative of the manzamine alkaloids, was isolated by Higa and co-workers in 1986.[9] This class of compounds has shown a variety of bioactivities.[10] Although **1** and its 8-hydroxy analogue (**2**) showed outstanding antimalarial activity both in vitro and in vivo compared to the currently utilized first line antimalarial drugs, chloroquine and artemesinin,[11] their toxicity limited their development as drugs. As a part of a continued investigation of the structure–activity relationship (SAR) and optimization studies of **1** against malaria, we prepared amide analogues of **1** for evaluation in vitro against chloroquine sensitive and resistant *Plasmodium falciparum* relative to cytotoxicity.

Nitration of **1** (Scheme 1) by $NaNO_2$ and trifluoroacetic acid (TFA) gave two nitro products: 6- (**3**) and 8-nitromanzamine A

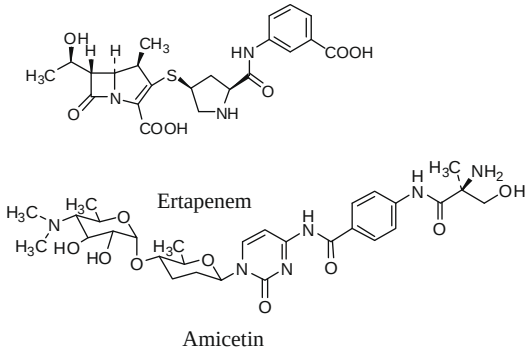
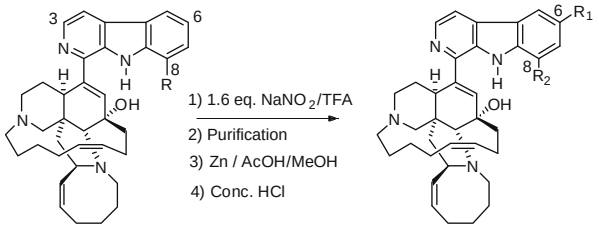


Figure 1. Drugs that possess aryl amide moieties.



Scheme 1. Nitration of manzamine A. (**1**) Manzamine A, R = H; (**2**) 8-hydroxymanzamine A. R = OH; (**3**) 6-nitromanzamine A, $R_1 = NO_2$, $R_2 = H$; (**4**) 8-nitromanzamine A, $R_1 = H$, $R_2 = NO_2$; (**5**) 6-aminomanzamine A, $R_1 = NH_2$, $R_2 = H$; (**6**) 8-aminomanzamine A, $R_1 = H$, $R_2 = NH_2$.

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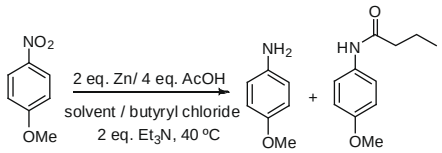
Table 1
Solvent optimization for reductive amidation reaction



1a 2a 3a

Entry	Solvent	Time (h)	Yield[a] (%)	
			2a	**3a**
1	MeOH	4	98	0
2	DCM	4	80	15
3	DMF	4	30	65
4	Toluene	4	60	37

All reactions were done using 1.0 mmol of 4-nitroanisole.
All reactions showed complete conversion of the starting material.
[a] Isolated yield.

(**4**). Zinc/acetic acid reduction of the nitromanzamines afforded the corresponding aminomanzamines (**5** and **6**), which were unstable even as HCl salts. This lack of stability created numerous challenges during amidation of the aminomanzamines. These difficulties were the driving force to explore an effective, practical, and gentle one-pot reductive amidation of nitroarenes.

Examples of a one-pot reductive amidation of nitroarenes have been reported. Watanabe uses $PtCl_2(PPh_3)_2$/tin(IV)chloride/CO/carboxylic acid as a reductive amidation system which requires high temperature (180 °C) and pressure (60 atm),[12] and is not applicable to sensitive and complex natural products.

Samarium diiodide has been used to reduce nitroarenes in the presence of a proton source to generate a nitrogen anion equivalent which can then be acylated with esters.[13] This method is valuable in regards to the use of esters as acylating agents. However the major disadvantage of this method is that the preformed nitrogen anion equivalent is basic enough to generate side reactions in complex natural products which normally have a diverse range of functional groups. Another disadvantage of using samarium diiodide is that it is sensitive to moisture, and requires highly dry reaction conditions. Limited examples for reductive acetamidation are reported. One example uses nucleophilic attack of thioacetate anion at the nitro group,[14] providing the acetamide derivative without the intermediate amine. This method could be expanded for the synthesis of amides other than acetamide, but it is not applicable to a complex structure with base sensitive functional groups such as **1,** in which the dehydration of the allylic 3° hydroxy group at C-12 is always obtained as a by-product in most of the base-

Table 2
Reductive amidation of several nitroarenes

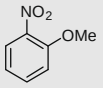
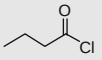
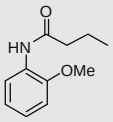
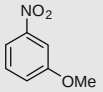
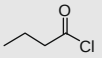
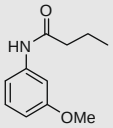
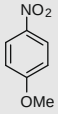
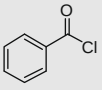
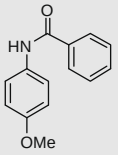
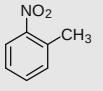
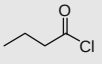
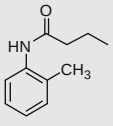
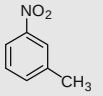
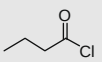
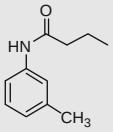
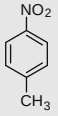
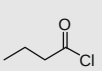
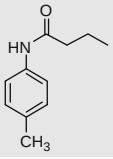
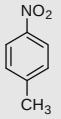
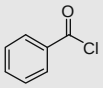
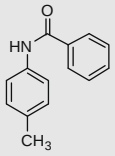
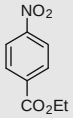
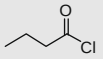
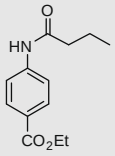
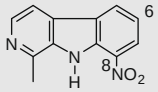
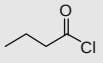
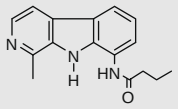
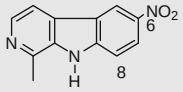
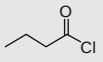
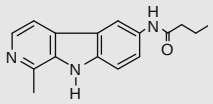
Entry	Starting material	Acyl chloride	Time (h)	Amide product	Yield[a] (%)
1			4.5		64
2			4		58
3			5		60
4			4		56
5			4		51
6			4.5		62

Table 2 (*continued*)

Entry	Starting material	Acyl chloride	Time (h)	Amide product	Yield[a] (%)
7			5		64
8			5.5		53
9			0.5		55[b]
10			0.5		58[b]

All reactions were done using 1.0 mmol of starting material.

[a] Isolated yields.

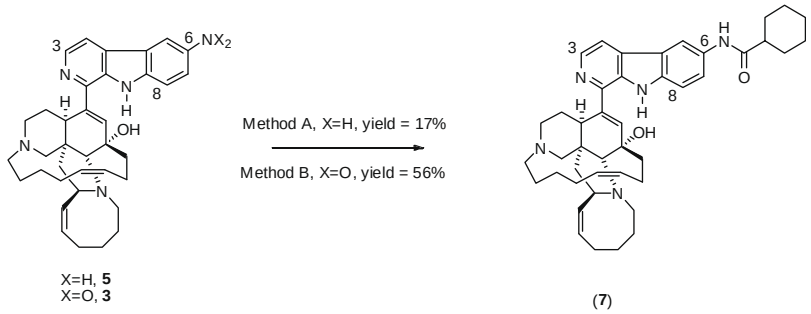
[b] Reactions were done using 0.4 mmol of nitroharmanes.

mediated reactions of **1**.[15] Kim has used zinc and acetic anhydride for the conversion of nitroarenes into N,O-diacetylated *N*-arylhydroxyamines in good yields. However, the acetamide yields were very low.[16] Furthermore, Kim reported high yields of the acetamide derivatives when nitroaromatics were treated with acetic anhydride and acetic acid catalyzed by indium, with trace yield of the diacetylated product.[17] These two methods, although showed selectivity to both products and high yields of each, are not applicable to manzamine A or related structures. Manzamine alkaloids have yielded unexpected rearranged products when treated with acetic anhydride.[18] We report here the reductive amidation of nitroarenes promoted by zinc and acetic acid as the reducing system and acyl chloride and triethylamine as the acylating agent in a one-pot approach. Application to the manzamine alkaloids is utilized as an example of the applicability of this method to complex natural products.

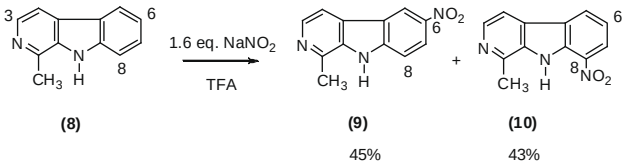
Reduction of the nitro group generally requires a protic solvent as a carrier of the hydrogen generated in situ. However, the amidation reaction using acyl chloride requires aprotic solvent as well as dry conditions to prevent a side reaction with the solvent. In addition, the amidation reaction using acyl chlorides requires basic conditions, in which the base will neutralize the hydrochloric acid liberated from the reaction as a by-product. Because of this contrast, we decided to explore the ability of adding 3° amine bases (triethylamine, Et_3N) in the reduction step, where equimolecular amounts of acetic acid and zinc are used, in addition to the acyl chloride. Once the amine is formed in situ, it will immediately react with the acyl chloride facilitated by the tertiary amine present in solution. Solvent optimization of this one-pot reaction was completed using 4-nitroanisole and butyryl chloride as a test reaction (Table 1).

DMF gives the best results, where the yield of the amide product obtained from the nitro compound was the same as that obtained from the corresponding amine. Using the optimized reaction conditions, we screened several nitro compounds with butyryl chloride as well as other acyl chlorides (Table 2). All the reactions showed 100% conversion of starting material to the corresponding amines and amide products, with moderate to good yield of the amide products.

After optimizing the reaction conditions, we investigated the applicability of this reaction to the synthesis of 6-cyclohexamidemanzamine A (**7**) (Scheme 2). This amide analogue was



Scheme 2. Amidation of **1**. Method A: 1.2 equiv CCC, 1.1 equiv Et_3N, cat. DMAP, THF, rt, 1 h; Method B: reductive amidation approach; no amine was observed in both methods.



Scheme 3. Nitration of harmane.

synthesized from **5** using the normal amidation reaction with a very low yield (17%). Also, this analogue showed potent antimalarial activity in vitro with an IC_{50} of 0.032 μM against the D6 clone of *P. falciparum* with no cytotoxicity up to 4.7 μM. It was surprising that the reductive amidation of **3** with cyclohexylcarbonyl chloride (CCC) runs smoothly and quickly (10 min) without the addition of Et_3N and with a significant improvement in yield (56%). A reasonable explanation is that nitromanzamines have two 3° amine bases, which likely accelerate the amidation reaction.

To validate this rationale, we utilized harmane (**8**) as a precursor to the synthesis of the closely related model compounds 6-nitroharmane (**9**) and 8-nitroharmane (**10**). Harmane (**8**) was nitrated using exactly the same conditions as **1** (Scheme 3) which gave **9** and **10** in 45% and 43% yields, respectively. Applying the same reductive amidation conditions to **9** and **10** without the addition of Et_3N did not give the amide products, even after 12 h of stirring. The amide products of **9** and **10** were obtained after the addition of Et_3N to the solution (Table 2, entries 9 and 10). These results clearly validated our explanation regarding the built in tertiary amine bases in manzamine alkaloids.

In conclusion, this is the first report of using 3° amine base in the reduction step of the nitro compounds in addition to the acid chloride in a one-pot approach to form the corresponding amide. The yields of the amides are reasonable for the model compounds however more significant is that the reaction conditions are very mild well tolerated with **1** and showed significant improvement in the yield of the amide analogues of **1**. This reaction is certain to have utility in the optimization studies of various natural product heterocyclic systems.

Acknowledgments

We thank Keith Hollis for valuable discussion and suggestions. Desmond Slade for GCMS analysis and Mahmoud ElSohly for GCMS instrumentation. Subagus Wahyuono at Gadjah Mada University is gratefully acknowledged for sample collections. We thank Shabana Khan and John Trott for in vitro antimalarial evaluation. This work was funded by NIH grants NCRR P20 RR021929 (Center of Research Excellence in Natural Products Neuroscience); NIAID 5RO1AI1036596; and an NIH research facilities improvement grant C06 RR-14503-01. A.E.W. gratefully thanks The Ministry of Higher Education of Egypt for a predoctoral fellowship. Also A.E.W thanks Triton BioPharma AG for a Triton fellowship.

Supplementary data

Supplementary data (detailed experimental information and the spectral data as well as copies of the ^1H NMR and ^{13}C NMR spectra for compounds **7**, **9**, **10** and (Table 2, entries 9 and 10) are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.061.

References and notes

1. *Merck Index*, 14th ed.; Budavari, S., Ed.; Merck, 2006; Vol. 397, p 3673.
2. Tsukinoki, T.; Tsuzuki, H. *Green Chem.* **2001**, *3*, 37–38.
3. Hodgson, H. H.; Whitehurst, J. S. *J. Chem. Soc.* **1945**, 202–204.
4. Nishimura, S. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 32–36.
5. Mendenhall, G. D.; Smith, P. A. S. *Org. Synth. Coll.* **1973**, *5*, 829–833.
6. Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 695–698.
7. Adkins, H.; Connor, R. *J. Am. Chem. Soc.* **1931**, 53.
8. Broadbent, H. S.; Slaugh, L. H.; Jarvis, N. L. *J. Am. Chem. Soc.* **1954**, *76*, 1519–1523.
9. Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 640–6405.
10. Peng, J.; Rao, K. V.; Choo, Y. M.; Hamann, M. T. In *Manzamine Alkaloids in Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH Verlag GmbH & Co KGaA: Weinheim, Germany, 2007. pp 189–232.
11. Yousaf, M.; Hammond, N. L.; Peng, J.; Wahyuono, S.; McIntosh, K. A.; Charman, W. N.; Mayer, A. M. S.; Hamann, M. T. *J. Med. Chem.* **2004**, *47*, 3512–3517.
12. Watanabe, Y.; Tsuji, Y.; Kondo, T.; Takeuchi, R. *J. Org. Chem.* **1984**, *49*, 4451–4455.
13. Wang, X.; Guo, H.; Xie, G.; Zhang, Y. *Synth. Commun.* **2005**, *34*, 3001–3008.
14. Bhattacharya, A.; Purohit, V. C.; Suarez, V.; Tichkule, R.; Parmer, G.; Rinald, F. *Tetrahedron Lett.* **2006**, *47*, 1861–1864.
15. Unpublished results with manzamine alkaloids.
16. Kim, B. H.; Jun, Y. M.; Suh, S. W.; Baik, W.; Lee, B. M. *J. Chem. Res. (S)* **1998**, 46–47.
17. Kim, B. H.; Han, R.; Piao, F.; Jun, Y. M.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2003**, *44*, 77–79.
18. El-Sayed, K. A.; Khalil, A. A.; Yousaf, M.; Labadie, G.; Kumar, G. M.; Franzblau, S. G.; Mayer, A. M. S.; Avery, M. A.; Hamann, M. T. *J. Nat. Prod.* **2008**, *71*, 300–308.