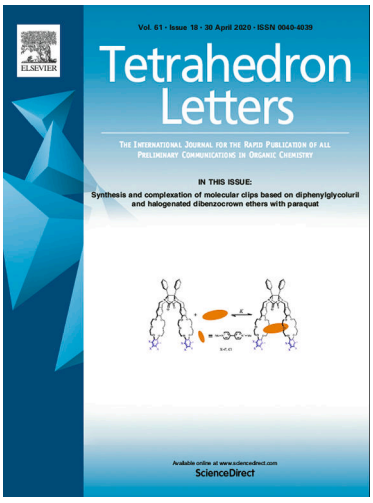
Journal Pre-proofs



Applicability of aluminum amalgam to the reduction of arylnitro groups

Paige J. Monsen, Frederick A. Luzzio

PII: S0040-4039(20)31074-1
DOI: https://doi.org/10.1016/j.tetlet.2020.152575
Reference: TETL 152575

To appear in: *Tetrahedron Letters*

Received Date: 25 September 2020
Revised Date: 11 October 2020
Accepted Date: 15 October 2020

Please cite this article as: Monsen, P.J., Luzzio, F.A., Applicability of aluminum amalgam to the reduction of arylnitro groups, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152575

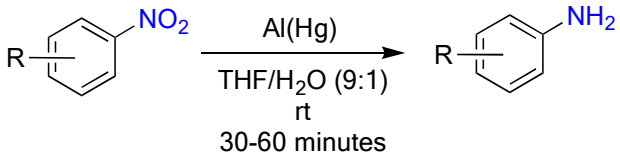
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Applicability of aluminum amalgam to the reduction of arylnitro groups

Leave this area blank for abstract info.

Paige J. Monsen and Frederick A. Luzzio



17 examples
-rapid
-mild
-selective
-inexpensive

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Applicability of aluminum amalgam to the reduction of arylnitro groups

Paige J. Monsen[a] and Frederick A. Luzzio[a,*]

[a] *Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky 40292, USA*

* Corresponding author. Tel.: +1-502-852-7323; fax: +1-502-852-8149; e-mail: faluzz01@louisville.edu

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aluminum amalgam
Arylnitro groups
Azides
Click chemistry
Reduction

ABSTRACT

An array of arylnitro compounds with various functionality were treated with freshly-prepared aluminum amalgam in THF/water solution and resulted in the corresponding arylamines. The Al(Hg)-mediated reductions are relatively rapid with consumption of the amalgam and disappearance of starting material occurring over 20-30 minutes. The workup of the reductions involves only removal of the insoluble by-products by filtration followed by concentration. Only in some cases is chromatography required to secure the pure product. The desired arylamines are furnished in quantities of 25-100 mg, which in some cases, could be taken on to the next reaction without further purification. Reductions of 4-nitrobenzyl derivatives of carbohydrates or nucleosides were selective in affording the corresponding 4-aminobenzyl products. To show applicability in click chemistry, selected aminobenzyl products are directly azidated to yield products that were then used in click reactions to afford the corresponding 1,2,3-triazoles.

1. Introduction

The reduction of arylnitro groups to the corresponding arylamino products constitutes a widespread and significant transformation in organic synthesis.[1-3] Considering the process is the most direct for the preparation of substituted aniline derivatives, the most desirable protocols allow for the presence of sensitive protecting groups as well as easily-reducible functional groups, heterocycles and heteroatoms. The reduction of arylnitro compounds can utilize a gamut of metals in conjunction with either hydrogen gas or water as well as metal/metalloid hydrides, in situ H_2 generation and redox and related processes.[3] However, a common denominator in most of the recent developments is the generation of less metallic and solvent waste which can favor greener and more economical and atom-efficient processes. As a consequence of searching for rapid, reliable, selective and inexpensive methods for the reduction of arylnitro groups to the corresponding arylamino groups under mild and neutral conditions, we were surprised to discover that there have been no reports or systematic studies of aluminum amalgam [Al(Hg)] in accomplishing such a routine process. Early studies by Keck[4,5] demonstrated the usefulness of aluminum amalgam in cleaving intramolecular N-O bonds to amino alcohols and resulted in a well-received protocol that was used as a pivotal step in many total syntheses (Figure 1).[6-10] Our later studies of aluminum amalgam [Al(Hg)]-mediated reductions included the conversions of imides to hydroxylactams[11] and nitroalkanols to the corresponding amino alkanols (Figure 1).[12,13] While the latter study was focused on minimizing both oxime formation and the retro-Henry (retro-aldol) side reactions, it did not reach beyond reduction of the nitroalkyl group inherent in the nitroalkanol functionality. However, during the course of reports describing three separate prostaglandin syntheses, the Corey group did in fact establish the applicability of Al(Hg) to the reduction of complex nitro aliphatic nitro intermediates.[14a-c] Interestingly, the Corey prostaglandin intermediates carried nitrile and dithiane functionality which survived the reduction.[14c] Later, the Keck-type reductions along with our results with nitroalkanols established the applicability for the generation of aminoalcohol intermediates. For any substrate, the advantage of the amalgam is that the reduction is run under neutral conditions. Hence, the employment of acid or basic extraction is also avoided and therefore an acylating agent for the amino group can be added to the reaction mixture at the conclusion of the reaction.[12] While our earlier experiences with nitroalkanol Al(Hg) reductions[12,13] demonstrated that power ultrasound was effective in increasing reactivity by dispersing the aluminum through shock wave-induced microfragmentation, we determined that sonication was not a necessary expedient in arylnitro reductions.

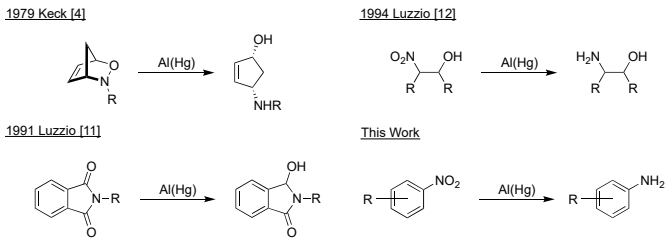


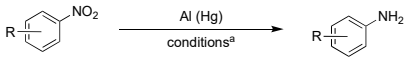
Figure 1. Al(Hg)-mediated reductive cleavage of nitrogen-oxygen bonds[4] and application of the process to reduce imides to hydroxylactams[11] and nitroalkanols.[12]

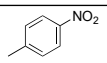
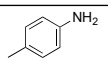
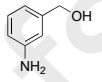
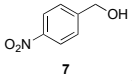
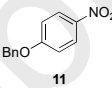
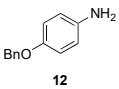
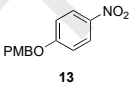
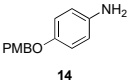
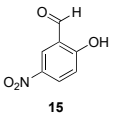
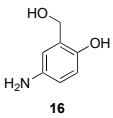
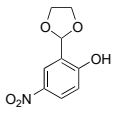
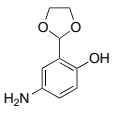
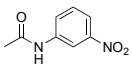
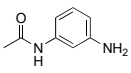
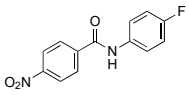
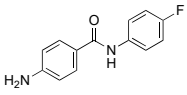
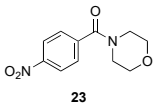
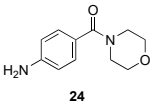
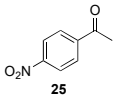
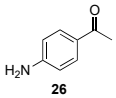
2. Results and discussion

The preparation and use of the aluminum amalgam used in the studies described herein is a simple reproducible process whereby food-grade aluminum foil is briefly treated with aqueous mercuric chloride solution and the amalgam is then introduced to a THF/water solution of the substrate to be reduced (See Supplementary data). Our initial examination of the Al(Hg) reduction of the arylnitro substrates was carried out under non-ultrasonic conditions and involved the transformation of simple monofunctionalized nitroaryls to establish reaction conditions and compatibility (Table 1). The nitrotoluene **1** (Table 1, entry 1) responded as anticipated and gave the p-toluidine **2** (>99%) after a simple filtration through a glass frit to remove oxidized aluminum species followed by concentration. The isomeric ortho, meta and para benzylic alcohols **3, 5** and **7** (Table 1, entries 2-4) were reduced to the corresponding arylamino benzylic alcohols **4, 6** and **8**, all in excellent yields with no cleavage of the benzylic oxygen bond or adjustment in acidity or basicity during the workup to secure the products. Despite the propensity for naphthalenes or substituted naphthalenes to reduce under electron-transfer conditions, 1-nitronaphthalene **9** (Table 1, entry 5) was cleanly reduced to 2-aminonaphthalene **10** (90%) without any ring reduction. However, using minimal amounts (2 weight-equiv) of Al(Hg) in the reduction of **9**, we observed a 74% yield of the corresponding hydroxylamine in contrast to complete conversion to the amine product using seven weight equivalents of aluminum. Benzylic ethers of nitrophenols **11** and **13** (Table 1, entries 6, 7) were reduced smoothly to the corresponding aminoaryl ethers **12** and **14** respectively (>99%) with no benzylic cleavage. Compatibility with carbonyl groups is always a concern when evaluating the selectivity of nitro group reductions, and along with aldehyde groups, simple substrates bearing amide, ketone and ester groups were evaluated. Reduction of 4-nitrosalicylaldehyde **15** (Table 1, entry 8) resulted in significant reduction to the aminobenzylic alcohol **16** (36%). However, protection of the aldehyde function of **15** through the acetal derivative **17** (Table 1, entry 9) followed by Al(Hg) reduction provided the corresponding aminoaryl acetal **18** (57%). N-Arylamide functionality remains intact during the Al(Hg) reduction as exemplified by the clean conversion of N-(3-nitrophenyl)acetamide **19** (Table 1, entry 10) to N-(3-aminophenyl)acetamide **20** (96%). Selectivity of the nitro group over amide groups bearing benzylic carbonyls was observed with substrates **21** and **23** (Table 1, entries 11, 12) thereby affording the corresponding aminoaryl amides **22** (80%) and **24** (94%) respectively. Similar to the reduction of aldehyde **15**, 4-Nitroacetophenone **25** (Table 1, entry 13) gave the corresponding aminoacetophenone **26** (43%) which was accompanied by carbonyl reduction to 1-(4-amino)phenylethanol.

The Al(Hg)-mediated reduction fits into click chemistry[15] schemes quite effectively whereby the products bearing the newly-formed arylamino group can be directly azidated after filtration of the reaction mixture to give the cycloaddition click partners (Table 2). When the geraniol p-nitrobenzoate **27** (Table 2, entry 1) was submitted to the reduction-azidation sequence ($NaNO_2/NaN_3/AcOH/H_2O$), the corresponding geranyl (4-azido)benzoate product **28** was obtained (27%) but accompanied with decomposition products. Quite possibly, the multiple sites of unsaturation of the geranyl moiety was not compatible with the azidization sequence. The 4-nitrobenzylic ether of 4-chloro-3-methylphenol **29** (Table 2, entry 2) was reduced followed by direct azidation to provide the 4-(azidobenzyl)chlorophenolic ether **30** (52%). No benzylic cleavage or hydrodechlorination by-products accompanied the desired product. The

Table 1. Al(Hg) reduction of various arylnitro substrates to corresponding arylamines.



Entry	Substrate	Product	Yield[b] (%)
1	 **1**	 **2**	>99
2	 **3**	 **4**	>99
3	 **5**	 **6**	>99
4	 **7**	**8**	>99
5	 **9**	 **10**	90
6	 **11**	 **12**	>99
7	 **13**	 **14**	>99
8	 **15**	 **16**	36
9	 **17**	 **18**	57
10	 **19**	 **20**	96
11	 **21**	 **22**	80
12	 **23**	 **24**	94
13	 **25**	 **26**	43

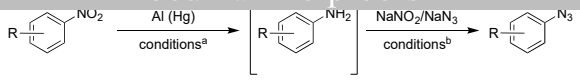
[a]Conditions: Al(Hg)/THF:H_2O (9:1)/rt, 30-60 min.

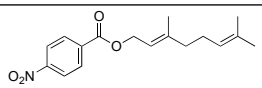
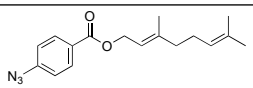
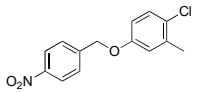
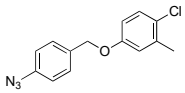
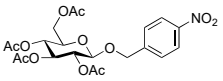
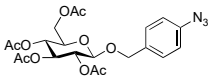
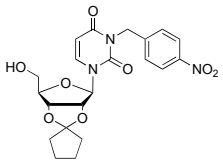
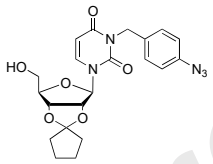
[b]Yields are for isolated purified products.

4-(nitrobenzyl)glycosyl tetraacetate **31** (Table 2, entry 3) responded well to the Al(Hg) reduction-azidation sequence and delivered the corresponding 4-(azidobenzyl)glycoside **32** (77%). Similarly, the N^3-4-(nitrobenzyl)cyclo-pentylidene uridine **33** (Table 2, entry 4) was submitted to reduction-azidation and provided the N^3-4-azidobenzyl derivative **34** (63%).

Further utilization of the 4-(azidobenzyl)-chlorophenolic ether **30**, the azidobenzyl glycoside **32**, and N^3-(azidobenzyl)nucleoside **34** in the copper-mediated 'click' cycloaddition reaction is easily facilitated and further

Table 2. Reduction-azidation of selected arylnitro derivatives to the corresponding arylazido products



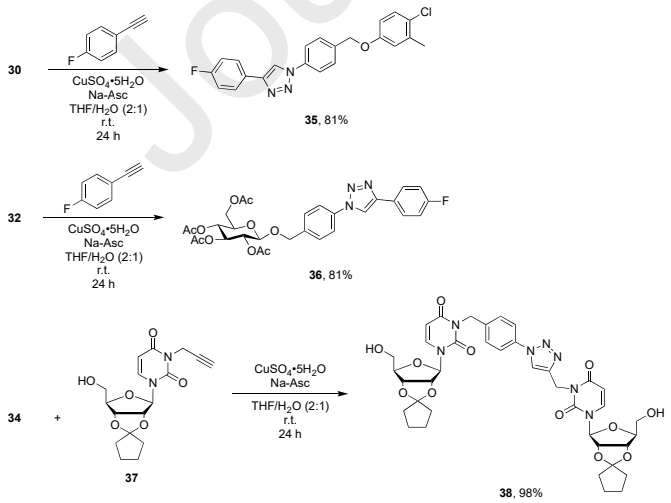
Entry	Substrate	Product	Yield[c] (%)
1	 **27**	 **28**	27
2	 **29**	 **30**	52
3	 **31**	 **32**	77
4	 **33**	 **34**	63

[a]Conditions: Al(Hg)/THF:H_2O (9:1)/rt, 30-60 min.

[b]Conditions: $NaNO_2/NaN_3$/AcOH:H_2O (1:1)/0 ˚C to rt, 30-90 min.

[c]Isolated purified yield of azido product over two steps from the starting nitro substrate.

demonstrates the utility of the Al(Hg) reduction-azidation sequence in delivering click products **35**, **36** and **38** (Scheme 1). Our choice of 4-ethynylfluorobenzene as the click partner for **35** and **36** was influenced by its desirable reactivity in an earlier study where it was utilized in the design of click biofilm inhibitors.[16,17] Thus, the 4-azidobenzyl ether **30** was reacted with 4-ethynylfluorobenzene in the presence of copper II sulfate pentahydrate and sodium ascorbate (THF/H_2O, 2:1) which provided the fluorophenyltriazole **35** (81%). The preparation of triazolylbenzylgycoside **36** exemplifies the generation of unique glycoconjugates which are made possible by the employment of diverse glycosyl azide derivatives.[18] Under the same conditions as the preparation of **35**, the 4-(azidobenzyl)glycosyl tetraacetate **32** was reacted with 4-ethynylfluorobenzene to afford the triazolylbenzylglycoside **36** (81%) (Scheme 1). The interest in bridged nucleosides as prodrugs and crosslinked oligonucleotides as transcription factor traps[19, 20] prompted us to evaluate the N^3-4-(azidobenzyl)uridine derivative **34** as a click co-reactant with the



Scheme 1. Click reactions of selected substrates **30**, **32**, **34** to give triazole products **35**, **36**, **38**.

Acknowledgments

N^3-propargyl derivative **37**. Accordingly, the click reaction of **34** and **37**, mediated with the same reagent system as **30**→**35** and **32**→**36** provided the N^3-$N^{3'}$ cross-linked triazole derivative **38** (98%). Click products **35, 36, 38** were characterized as the 1,4-'anti'-substituted triazoles in which the regiochemistry is consistent with the copper (I)-catalyzed mechanism.[21]

3. Conclusion

In summary, the Al(Hg) reduction of arylnitro compounds to the corresponding arylamines represents a significant departure from established methods such as metal hydride, catalytic hydrogenation or in situ hydrogen generation. The reduction of selected substrates demonstrates the varied applicability of the Al(Hg) system-especially during the course of a process wherein the product is directly taken on to the next reaction. The aluminum amalgam protocol is particularly useful in click chemistry whereby the amine product is directly taken on to the azide cycloaddition partner. From our vantage point, the lone drawback associated with the use of aluminum amalgam is the employment of mercury (II) chloride in its preparation. The toxicity of mercury salts is well-known,[22] and the use of many heavy metal-derived reagents precludes substantial scale-up in both research and industrial settings. Despite the toxicity of many mercury-derived systems, however, they will always find use in situations in which procurement of the target compound is of highest priority.[23]

Funding in part was provided by a University of Louisville Dissertation Completion Fellowship and NIH/NIDCR 1R01DE023206. Acknowledgement is made to the NSF (CHE1726633) for support of the Indiana University Mass Spectrometry Facility.

References and notes

1. Smith, M. B. *Compendium of Organic Synthetic Methods*; Wiley: New York, 2014; Vol. 13, pp 299-301.
2. Larock, R. C. *Comprehensive Organic Transformations-A Guide to Functional Group Transformations*; 2nd Ed.; Wiley: New York, 1999; pp 821-828. doi:10.1039/c5ra10076c
3. Kadam, H. K. Tilve, S. G. RSC Adv. 5 (2015) 83391-83407.

Commun. 9 (1979) 281-286. doi:10.1080/00397917908064153
5. Fieser, M.; Danheiser, R. L.; Roush, W. R. *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley: New York, 1981; Vol. 9, pp 449.

6. Al-Saad, D. Memeo, M. G. Quadrelli, P. ChemistrySelect 2 (2017) 10340-10346. doi:10.1002/slct.201702059
7. Savion, M. Memeo, M. G. Bovio, B. Grazioso, G. Legnani, L. Quadrelli, P. Tetrahedron 68 (2012) 1845-1852. doi:10.1016/j.tet.2011.12.086
8. Hudlicky, T. Olivo, H. F. J. Am. Chem. Soc. 114 (1992) 9694-9696. doi:10.1021/ja00050a079
9. Walts, A. E. Roush, W. R. Tetrahedron 41 (1985) 3463-3478. doi:10.1016/S0040-4020(01)96701
10. Oppolzer, W. Francotte, E. Battig, K. Helv. Chim. Acta 64 (1981) 478-481. doi:10.1002/hlca.19810640212
11. Luzzio, F. A. O'Hara, L. C. Synth. Commun. 20 (1990) 3223-3234. doi:10.1002/chin.199115162
12. Luzzio, F. A. Fitch, R. W. Tetrahedron Lett. 33 (1994) 6013-6016. doi:10.1016/0040-4039(94)88062-X
13. Luzzio, F. A. Fitch, R. W. J. Org. Chem. 64 (1999) 5485-5493. doi:10.1021/jo990293i
14. (a) Corey, E. J.; Vlattas, I.; Harding, K. J. Am. Chem. Soc, 91 (1969) 535-536 (b) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding, K. J. Am. Chem. Soc. 90 (1968) 3247-3248. (c) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter R. E. K. J. Am. Chem. Soc. 90 (1968) 3245-3247.
15. Mocherla, V. P. Colasson, B. Lee, L. V. Roper, S. Sharpless, K. B. Wong, C. H. Kolb, H. C. Angew. Chem. Int. Ed. 44 (2005) 116-120. doi:10.1002/slct.201702059
16. Patil, P. C. Tan, J. Demuth, D. R. Luzzio, F. A. Bioorg. Med. Chem. 24 (2016) 5410-5417. doi:10.1016/j.bmc.2016.08.059
17. Patil, P. C. Tan, J. Demuth, D. R. Luzzio, F. A. Med. Chem. Commun. 10 (2019) 268-279. doi:10.1039/c8md00405f
18. Tiwari, V. K. Mishra, B. B. Mishra, K. B. Mishra, N. Singh, A. S. Chen, X. Chem. Rev. 116 (2016) 3086-3240. doi:10.1002/slct.201702059
19. Nakane, M. Ichikawa, S. Matsuda, A. J. Org. Chem. 73 (2008) 1842-1851. doi:10.1021/jo702459b
20. Hatlelid, J. Benneche, T. Undheim, K. Acta Chem. Scand. 52 (1998) 1270-1274. doi:10.3891/acta.chem.scand.52-1270
21. Meldal, M. Tornøe, C. W. Chem. Rev. 108 (2008) 2952-3015. doi:10.1021/jo702459b
22. Egorova, K. S. Ananikov, V. P. Organometallics 36 (2017) 4071-4090. doi:10.1021/acs.organomet.7b00605
23. Fantuzzi, F. Synlett 25 (2014) 1043-1044. doi:10.1055/s-0033-1340958

Supplementary Data

Supplementary data features detailed experimental procedures, characterization data (^{1}H and ^{13}C NMR, FTIR, and HRMS data), and copies of spectra is provided.