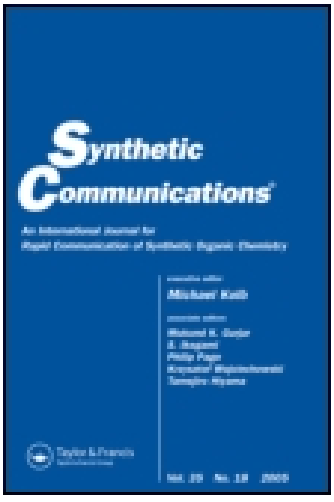


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Preparation and Purification of Desethylamiodarone Hydrochloride

Anthony N. Lucas [a], Mehmet Tanol [a], Michelle P. McIntosh [a] & Roger A. Rajewski [a]
[a] Center for Drug Delivery Research, University of Kansas, Lawrence, Kansas, USA
Published online: 23 Nov 2006.

To cite this article: Anthony N. Lucas, Mehmet Tanol, Michelle P. McIntosh & Roger A. Rajewski (2006) Preparation and Purification of Desethylamiodarone Hydrochloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:22, 3371-3376, DOI: 10.1080/00397910600941406

To link to this article: http://dx.doi.org/10.1080/00397910600941406

Synthetic Communications®, 36: 3371–3376, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600941406

Preparation and Purification of Desethylamiodarone Hydrochloride

Anthony N. Lucas, Mehmet Tanol, Michelle P. McIntosh, and Roger A. Rajewski
Center for Drug Delivery Research, University of Kansas, Lawrence, Kansas, USA

Abstract: Reaction of the free base of amiodarone with 1-chloroethyl chloroformate in toluene gives desethylamiodarone, which can be easily purified and converted to the hydrochloride salt.

Keywords: Amiodarone, chloroethyl chloroformate, dealkylation, desethylamiodarone, metabolite

INTRODUCTION

Amiodarone [(2-butylbenzofuran-3-yl) (4-[2-(diethylamino) ethoxy)]-3,5-diiodophenyl)methanone] is indicated for the treatment of acute and chronic atrial and ventricular arrhythmias in humans[1] and is seeing a resurgence of use for atrial fibrillation.[2,3] Both amiodarone and its major metabolite, desethylamiodarone [(2-butylbenzofuran-3-yl)(4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl)methanone],[4] are pharmacologically active,[5–7] and both compounds have been implicated in the prolongation of the duration of activation and recovery of the ventricular myocardium (QT interval),[8–12] which is a major side effect of chronic amiodarone administration. Desethylamiodarone is not commercially available, thereby limiting investigation into the in vivo behavior of both amiodarone and desethylamiodarone. The present work describes a facile method to prepare desethylamiodarone from the commercially available amiodarone hydrochloride salt. The method for de-ethylation of

Received in the USA April 20, 2006
Address correspondence to Roger A. Rajewski, Center for Drug Delivery Research, University of Kansas, Lawrence, KS 66047, USA. E-mail: rajewski@ku.edu

amiodarone to give desethylamiodarone is based on the work of Olofson et al. for the dealkylation of *N*-ethylpiperidine, *N*,*N*-diethylaniline, and various drugs with l-chloroethyl chloroformate.[13]

During our evaluation of the optimal reagents and conditions for generation of desethylamiodarone, we evaluated various chloroformic acid derivatives for their ability to dealkylate amiodarone. 1-Chloroethyl chloroformate proved to be the only chloroformic acid derivative of the compounds we studied that provided facile dealkylation. In addition to the work of Olofoson et al., this reagent has previously been used to prepare the *N*-demethylated metabolites of tamoxifen,[14] promazine, levomepromazine, orphenadrine, clomipramine and chloroprothixene,[15] various erythromycins,[16] and zopicione.[17] The mild reaction conditions involved when using 1-chloroethyl chloroformate for dealkylation of tertiary amines is especially useful for compounds with other acid labile functional groups.

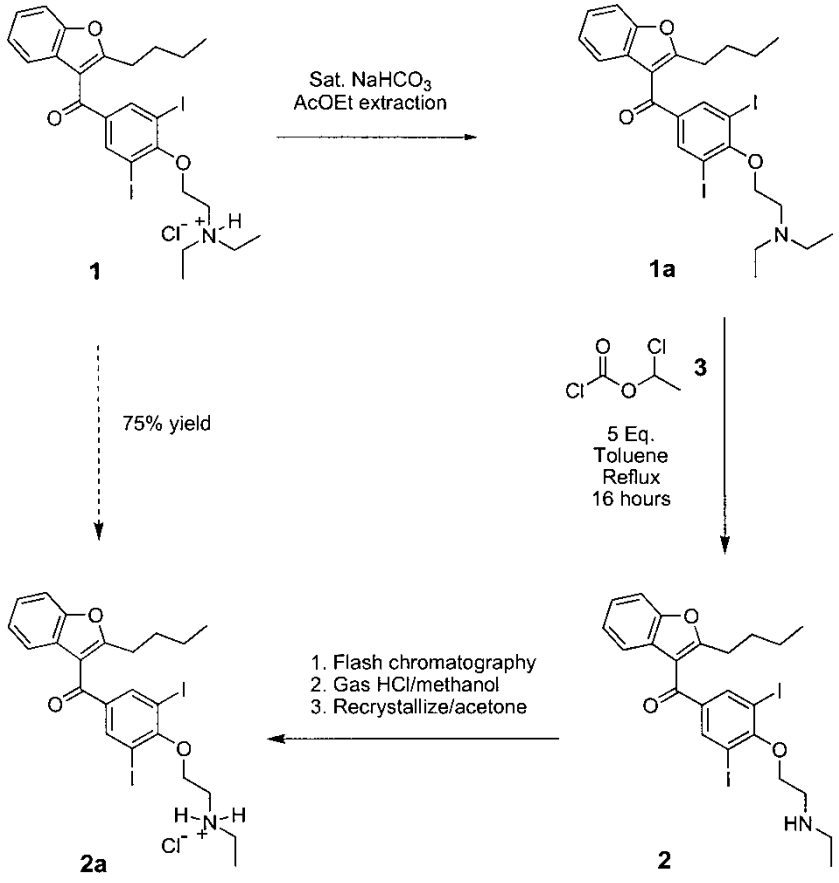
RESULTS AND DISCUSSION

Commercially available amiodarone hydrochloride (**1**) was converted to the free base (**la**) in saturated aqueous sodium bicarbonate, followed by extraction into ethylacetate Scheme 1. The ethylacetate solution was dried with sodium sulfate and filtered, and **la** was isolated by rotary evaporation of the solvent. Refluxing **la** and 1-chloroethyl chloroformate (**3, 5** equivalents) in toluene for 16 h resulted in nearly quantitative conversion of **1a** to desethylamiodarone (**2**) with minimal side-product formation. The rate of the reaction was enhanced with increased equivalents of **3**; however, the amount of by-products increased also.

Various other chloroformic acid derivatives were also evaluated for conversion of **la** to **2**. None of the seven other chloroformic acid derivatives attempted (Table 1) resulted in formation of **2**. For those derivatives that provided evidence of a stable tertiary or quarternary carbamate intermediate (liquid chromatography with mass detection, LC/MS analysis) followiong 16 h at reflux, additional workup in solution with bubbling HCI gas did not convert the carbamates to **2**, and all the intermediates were recovered unchanged.

Because **2a** was to be used in vivo studies and as an analytical standard, having a pure and well-characterized product was important. To obtain a pure product, the crude product **2** was subjected to flash chromatography and converted to **2a** with gas HCI. Compound **2a** was recrystallized twice to give the highly pure product in good yield (75%) based on the original amount of **1**. The identity of **2a** was confirmed with ^{1}H and ^{13}C NMR, elemental analysis, and FAB mass-spectral analysis. The purity of **2a** was determined using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fisher titration, and reverse-phase LC/MS.

The NMR spectra of **2a** were in excellent agreement with the corresponding spectra of **1** and were consistent with the loss of one ethyl group in **2a**. Fast atom bombardment (FAB) positive mass spectral analysis gave a



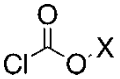
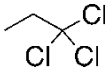
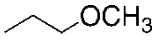
Scheme 1.

major M+1 ion peak of 618.1 amu, consistent with the exact mass of **2**. Compound **2a** did not contain residual volatile solvents based on Karl Fisher and TGA analysis. It exhibited a single sharp endotherm on DSC analysis and a single peak on LC/MS analysis with an M+1 peak of 618 amu, indicating the high purity of the product. The procedure described provides for the facile preparation of pure **2a** from **1** in high yield.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. FAB mass-spectral analysis was performed on a VG (MicroMass) ZAB HS spectrometer in a matrix of nitrobenzyl alcohol in

Table 1. Chloroformic acid derivatives attempted for the de-ethylation of amiodarone

	Desethyl-amiodarone	Stable intermediate	No reaction
	+		
		+	
		+	
		+	
		+	
		+	+
			+
			+

Note: Reaction conditions: 5 eq. choloroformic acid derivative refluxed in toluene for 16 h.

methanol. TGA and DSC analyses were performed on a Perkin Elmer TGA7 gravimetric analyzer and Pyris 1 calorimeter, respectively. Karl Fisher analysis was performed on a Brinkman 652 KF-coulometer. For LC/MS analysis, the sample was fractionated on a Zorbax column (5 μm, SB-18, 2.1 × 50 mm) using a modular Shimadzu system consisting of a LCMS-2010 detector in elctrospray positive mode, a SIL-10 ADVP auto injector, LC-10 ADVP pumps, DGV-14A degasser, and SL-10AVP system controller, with data collection and analysis performed by LCMS solution ver. 2.04 software. The mobile phase consisted of 0.4:99.6 parts ammonium hydroxide (30%)–methanol at a flow rate of 200 μL/min.

The free base **1a** was prepared from commercially available **1** by dissolving **1** (3.0 gm, 4.4 mmol) in saturated aqueous sodium bicarbonate (200 mL) and mixing the resulting solution vigourously with ethylacetate (200 mL) for 30 min. The organic layer was isolated, dried with sodium sulfate, filtered, and evaporated to dryness to give a yellow liquid. The residue was dissolved in toluene (10 mL) and 1-chloroethyl chloroformate (5 equivalents; 2.4 mL) was added with stirring. The mixture was refluxed for 16 h, cooled to room

temperature, and evaporated to dryness under vacuum. The resulting residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was isolated, dried with sodium sulfate, filtered, and evaporated to dryness under vacuum. The crude product was purified by flash chromatography on silica gel via elution of impurities with ethyl acetate–hexanes (10:90 V/V) followed by elutuion of **2** with methanol. Compound **2** was converted to **2a** by bubbling HCl gas through the pooled methanol fractions that were then evaporated to dryness. The product were recrystallized twice in acetone to give 2.17 g of **2a** (75% yield) as a white solid. The ^{1}H and ^{13}C NMR (400 MHz, $CDC1_3$) spectra of **2a** were compared to those of **1**, and chemical shifts were within 0.1 ppm. The integration of the ethyl protons (3.47 and 1.58 ppm) corresponds to the loss of one ethyl group in **2a**. FAB positive: M+l peak 618.1 amu; **2** exact mass 616.99 amu. Karl Fisher analysis: 0% water. DSC analysis: single, sharp endotherm at 186.7°C. Anal. calcd. for $C_{23}H_{26}ClI_2NO_3$: C, 42.26; H, 4.01; N, 2.14. Found: C, 42.47; H, 4.00; N, 2.22.

ACKNOWLEDGMENT

This work was supported in part by a grant from the Kansas Technology Enterprise Corporation through the Centers for Excellence Program.

REFERENCES

1. Malpartida, F.; Mola, M.; Huguet, R.; Sala, J.; Noguera, J.; Cordeiro, B. Clinical evaluation of amiodarone hydrochloride as an anti-arrhythmia agent. *Rev. Md. Univ. Navarra* **1975**, *19*, 143–149.
2. Roy, D.; Talajic, M.; Dorian, P.; Connolly, S.; Eisenberg, M. J.; Green, M.; Kus, T.; Lambert, J.; Dubuc, M.; Gagne, P.; Nattel, S.; Thibault, B. Amiodarone to prevent recurrence of atrial fibrillation: Canadian trial of atrial fibrillation investigators. *N. Engl. J. Med.* **2000**, *342*, 913–920.
3. Shinagawa, K.; Shiroshita-Takeshita, A.; Schram, G.; Nattel, S. Effects of anti-arrhythmic drugs on fibrillation in the remodeled atrium: Insights into the mechanism of the superior efficacy of amiodarone. *Circulation* **2003**, *107*, 1440–1446.
4. Flanagan, R. J.; Storey, G. C.; Holt, D. W.; Farmer, P. B. Identification and measurement of desethylamiodarone in blood plasma specimens from amiodarone-treated patients. *J. Pharm. Pharmacol.* **1982**, *34*, 638–643.
5. Nattel, S. Pharmacodynamic studies of amiodarone and its active n-desethyl metabolite. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 771–777.
6. Kharidia, J.; Eddington, N. D. Effects of desethylamiodarone on the electrocardiogram in conscious feely moving animals: Pharmacokinetic and pharmacodynamic modeling using computer-assisted radio telemetry. *Biopharm. Drug Dispos.* **1996**, *17*, 93–106.

7. Pollak, P. T.; Sharma, A. D.; Carruthers, S. G. Correlation of amiodarone dosage, heart rate, QT interval and corneal microdeposits with serum amiodarone and desethylamiodarone concentrations. *Am. J. Cardiol.* **1989**, *64*, 1138–1143.
8. Torres, V.; Tepper, D.; Flowers, D.; Wynn, I.; Lam, S.; Keefe, D.; Miura, D. S.; Somberg, J. C. QT prolongation and the antiarrhythmic efficacy of amiodarone. *J. Am. Coll. Cardiol.* **1986**, *7*, 142–147.
9. Stark, G.; Stark, U.; Windisch, M.; Vicenzi, M.; Eggemeich, U.; Nagl, S.; Kral, K.; Pilger, E.; Tritthart, H. A. Comparison of acute electrophysiological effects of amiodarone and its metabolite desethylamiodarone in Langendorff perfused guinea pig hearts. *Basic Res. Cardiol.* **1991**, *86*, 136–147.
10. Baerman, J. M.; Annesley, T.; DiCarlo, L. A., Jr.; Foley, M. K.; Nicklas, J. M.; Crevey, B. J.; Morady, F. Interrelationships between serum levels of amiodarone, desethylamiodarone, reverse t3 and the QT interval during long-term amiodarone treatment. *Am. Heart. J.* **1986**, *111*, 644–648.
11. Burgess, C. D.; Siebers, R. W.; Purdie, G. L.; Taylor, C.; Maling, T. J. The relationship between the QT interval and plasma amiodarone concentration in patients on long-term therapy. *Eur. J. Clin. Pharmacol.* **1987**, *33*, 115–118.
12. Cubeddu, L. X. QT prolongation and fatal arrhythmias: A review of clinical implications and effects of drugs. *Am. J. Ther.* **2003**, *10*, 452–457.
13. Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. A new reagent for the selective, high-yield n-dealkylation of tertiary-amines—improved syntheses of naltrexone and nalbuphine. *J. Org. Chem.* **1984**, *49*, 2081–2082.
14. da Costa, G. G.; McDaniel-Hamilton, L. P.; Heflich, R. H.; Marques, M. M.; Beland, F. A. DNA adduct formation and mutant induction in-Sprague-Dawley rats treated with tamoxifen and its derivatives. *Carcinogenesis* **2001**, *22*, 1307–1315.
15. Pelander, A.; Ojanpera, I.; Hare, T. A. Preparation of n-demethylated drug metabolites for analytical purposes using 1-chloroethyl chloroformate. *Forensic Sci. Int.* **1997**, *85*, 193–198.
16. Hengeveld, J. E.; Gupta, A. K.; Kemp, A. H.; Thomas, A. V. Facile n-demethylation of erythromycins. *Tetrahedron Lett.* **1999**, *40*, 2497–2500.
17. Hong, Y. P.; Bakale, R. P.; Fang, Q. K.; Xiang, T. J.; McConville, F. X.; Senanayake, C. H.; Wald, S. A. Synthesis of enantiomerically pure desmethylzopiclone and determination of its absolute configuration. *Tetrahedron: Asymmetry* **2000**, *11*, 4623–4627.