Efficient Large-Scale Radical Deoxygenation in Alcoholic Solvents Using Sodium Hypophosphite and a Phase-Transfer Agent: Application to Erythromycins

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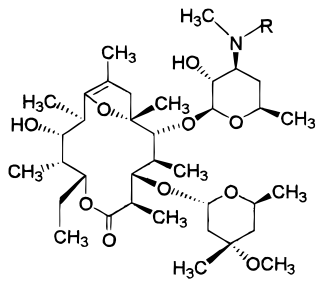
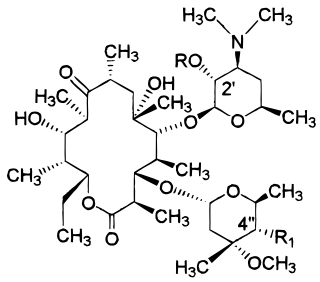
ABT-229 (**1**) is an erythromycin derivative that lacks antibacterial activity but is a potent motilin receptor agonist.[1] As such, **1** is a member of the class of compounds known as motilides,[2] which have been tested in clinical trials as potential prokinetic agents for the treatment of diabetic gastroparesis, gastroesophageal reflux disease, and functional dyspepsia.



1 R=Et

5 R=Me



2 R=H, R_1=OH
3 R=H, R_1=H
4 R=Ac, R_1=OC(S)Im
6 R=H, R_1=OC(S)OC_3H_7
7 R=Ac, R_1=OC(S)OC_3H_7

A key step in the synthesis[1] of **1** involves the conversion of erythromycin B (**2**) to 4″-deoxyerythromycin B (**3**). This entails selective protection of the more reactive 2′-hydroxy group of **2**, followed by functionalization of the 4″-position as the imidazole thionocarbamate (**4**). Barton deoxygenation[3] with tri-*n*-butyltin hydride in toluene at 100 °C, followed by 2′-*O*-acetate removal with methanol, gives the desired intermediate **3**.

Reactions at such high temperatures, in the presence of organotin species, invariably result in the formation of degradation products. In addition, extensive purification steps are needed to remove residual, toxic, organotin byproducts in order to meet regulatory stipulations. There are also engineering challenges, on a large scale, associated with the rapid quench of the very fast reaction in order to minimize degradation.

In the course of developing a viable commercial process for the synthesis of **1**, we investigated alternate methodologies for the deoxygenation of **4**. There have been numerous accounts of the search for other hydrogen atom sources as an alternative to tri-*n*-butyltin hydride. These include the use of silanes,[4] dialkyl phosphites,[5] and hypophosphorous acid and its organic salts.[5] The deoxygenation of erythromycins using organic salts of hypophosphorous acid and 2,2′-azobisisobutyronitrile (AIBN) has been reported.[5b] We subsequently reported an improved procedure for the synthesis of **1** via deoxygenation with hypophosphorous acid in ethanol using a new radical initiator 4,4″-azobis(4-cyanovaleric acid) (ACVA).[6] Byproducts of this reaction are **5**, from intramolecular acetalation/dehydration at C-9 and **2**, from competing hydrolysis of the thionocarbamoyl imidazole. On a laboratory scale, the formation of **5** was adequately controlled by the use of excess triethylamine while hydrolysis was minimized by using a high solvent-to-substrate ratio (20 mL/g substrate). The use of large volumes of solvent is, however, impractical on a large scale as it reduces the throughput in the synthetic sequence. On a scale starting from 5 kg of **4**, a significant, albeit manageable, amount of **6** was formed during the long ethanol distillation at the end of the reaction. This is presumably due to loss of triethylamine as an azeotrope thereby leading to acidic conditions. A way around this problem would have been to use organic salts of H_3PO_2, but these reagents gave rather poor yields, as the reactions were sluggish and the pH tended to drop during the process. This may have been due to dissociation of the salts under the reaction conditions.

Inorganic salts of H_3PO_2 are readily available and inexpensive and should be more stable. However, according to literature precedents, such salts have not been successfully used in deoxygenation reactions.[5a] We reasoned that if conditions were developed in which a homogeneous mixture of the salt, starting material, and

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Table 1

entry	solvent	PTA	initiator	method	time to completion (min)	yield (%)
1	EtOH	TBAH	ACVA	III	120	70.7
2	PrOH	TBAH	ACVA	III	50	94.0
3	*i*-PrOH	TBAH	ACVA	III	120	92.4
4	2ME		ACVA	III	20	80.0
5	2ME	TBAH	ACVA	III	10	95.1
6	PrOH	TBAH-2	ACVA	III	70	83.4
7	PrOH	TBAH	ACVA	III	70	89.3
8	PrOH	BTAH	ACVA	III	60	90.7
9	PrOH	TMEA	ACVA	III	70	87.8
10	PrOH	TBPB	ACVA	III	60	90.1
11	2ME		ACVA	I	40	83.6
12	2ME	TBPB	ACVA	II	20	95.0
13	2ME		AIBN	I	20	77.2
14	2ME	TBPB	AIBN	II	10	75.3
15	2ME	TBPB	ACCN	II	60	71.5
16	2ME	TBPB	AMHP	II	60	86.1

radical initiator were attained, it may be possible to develop an inexpensive and robust process for the preparation of **3**. We therefore studied the effect of solvents and phase-transfer agents on the conversion of **4** to **3** using NaH_2PO_2 and different radical initiators. We hereby report the results of our studies, which have yielded an efficient and robust process for the synthesis of **3** on a multi-kilogram scale.

Results and Discussion

The effect of solvents was first studied using ACVA with or without the addition of 1 M tetrabutylammonium hydroxide in methanol (TBAH) as the phase-transfer agent (PTA). In EtOH, PrOH, and *i*-PrOH in which NaH_2PO_2 was only sparingly soluble, reactions without the PTA were quite sluggish (>3 h completion time), yielded a number of byproducts, and were, in some cases, intractable. In the presence of TBAH, however, these reactions proceeded smoothly to afford 71 to 94% yields of **3** (entries 1−3, Table 1). The reaction was significantly faster in the higher boiling PrOH. 2-Methoxyethanol (2-ME) gave a more homogeneous reaction mixture and cleanly yielded **3** (20 min, 80%) in the absence of TBAH (entry 4). In the presence of TBAH, the reaction in 2ME was accelerated (10 min) and afforded a 95% yield (entry 5). This observation suggests that solubility of reactants in the solvent or homogeneity of the reaction mixture is an important parameter in this reaction. Furthermore, polar protic solvents are required, as aprotic solvents, such as dioxane, propyl actetate, acetonitrile, and toluene failed to give any useful reactions, with or without PTAs.

The reaction in PrOH also gave a new thionocarbamate byproduct, which we characterized as the *n*-propyl derivative (**6**), obviously a product of thionoimidazole solvolysis. We later synthesized 2′-*O*-acetyl-4″-*O*-(1-propionoxy)thionocarbonyl erythromycin B (**7**) and demonstrated that it did not undergo deoxygenation at the 4″-position, under the conditions of these experiments. Hence, the alcoholic solvents did not participate in these reactions, but merely served to attain the solubility of the reactants and stability of the radical anion necessary for the deoxygenation with the inorganic salt. A further observation is that whereas NaH_2PO_2 may not be the only inorganic hypophosphite salt that can effect this reaction, it is important that the salt be, at least, sparingly soluble in the alcoholic solvent. Thus, $MnHPO_2$, which is insoluble in the alcohols used in this study, failed to yield **3** under these conditions.

Other PTAs that were investigated were TBAH as a 40% solution in methanol (TBAH-2), benzyltriethylammonium hydroxide as a 40% solution in methanol (BTAH), tris[2-(2-methoxyethoxy)ethylamine (TMEA), and tetra-*n*-butylphosphonium bromide (TBPB). Because it is a nonbasic PTA, reactions involving TBPB required additional base (method II). As shown in Table 1 (entries 6−10), all PTAs investigated gave good yields of **3**, inferring that the nature of the PTA is of little consequence in this procedure.

We also investigated the effect of other radical initiators. In this study, 2ME was used as solvent, with or without TBPB as the PTA. We again observed that AIBN and ACVA, which are both soluble in 2ME, gave good yields of **3** in the absence of TBPB. Addition of the PTA nonetheless accelerated the reaction, cutting completion time in half (entries 11−13). On the other hand, azobis(cyclohexanecarbonitrile) (ACCN) and 2,2′-azobis[2-methyl-*N*-(2-hydroxyethyl)propionamide) (AMHP), which have very little solubilities in 2ME, required addition of PTA to yield tractable reactions in reasonable time (entries 15 and 16). The attempted deoxygenation with benzoyl peroxide in 2ME was unsuccessful.

We conclude that a versatile but robust procedure has been developed for deoxygenations, which can be used economically on a large scale. Thus, method III was used to convert 15 kg (17.2 mol) of **4** to **3** (30 min, 90% yield after crystallization from $MeOH/H_2O$), toward preparation of **1**. Furthermore, the process may be of general utility in the deoxygenation of compounds bearing acid sensitive functionalities. As an example, 1,2:5,6-di-*O*-isopropylidine-3-*O*-(pentafluorophenoxy)thionocarbonylglucofuranose was efficiently deoxygenated (10 min, 69% yield) in 2ME, using TBAH as the PTA.

Experimental Section

Compound **4** was prepared as previously described.[1] All solvents were reagent grade. ACVA and AMHP were from Wako Chemicals USA, Inc. (Richmond, VA), while AIBN and ACCN were obtained from Aldrich Chemical Co., Inc. (Milwaukee, WI). TBAH-2, BTAH, and TBPB were obtained from Lancaster Chemicals (Windham, NH), while TBAH and TMEA were purchased from Aldrich. Sodium hypophosphite monohydrate was purchased from Aldrich/Fluka Chemicals (Milwaukee, WI) and from Occidental Chemical Corp. Reactions were monitored by HPLC for the disappearance of **4**. Unless otherwise stated, the yield of **3** was determined by HPLC of the crude product obtained after deacetylation in MeOH. Microanalyses were performed by Robertson Microlit Laboratories, Inc. (Madison, NJ).

Method I. Example of a Reaction without a Phase-Transfer Agent. 4,4′-Azobis-(4-cyanovaleric acid) (1.61 g, 5.75 mmol) was dissolved in cold 2-methoxyethanol (10 mL) and the pH adjusted to 8.0 with Et_3N. A portion (2/3) of the above solution was added, under nitrogen, to a refluxing mixture of NaH_2PO_2 (3.05 g, 28.75 mmol) in the solvent (50 mL). A warm (45 °C) solution of **4** (5 g, 5.75 mmol) in the desired solvent (15 mL) was added to the refluxing mixture. The remainder of the initiator solution was added portionwise to the reaction mixture over 40 min and the reaction monitored to completion. The reaction mixture was cooled to 45 °C, pH was adjusted to 8 by addition of 10% aqueous $NaHCO_3$, and solvents were removed in vacuo. The residue was partitioned with EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated and further washed with H_2O (50 mL) and evaporated in vacuo to afford a residue that was redissolved in MeOH (25 mL). The solution was heated to 50 °C for 8−10 h and MeOH removed to yield crude **3**.

Method II. Example of a Reaction Using a Nonbasic Phase-Transfer Agent. NaH_2PO_2 (6.1 g, 57.5 mmol) and TBPB (1.95 g, 5.75 mmol) were suspended in 2-methoxyethanol (50 mL), and the pH was adjusted to between 7 and 8 with triethylamine. The mixture was heated to 95 °C under N_2. A portion (1/2) of the initiator, prepared by dissolving ACVA (1.61 g, 5.75 mmol) in 2-methoxyethanol (15 mL) and adjusting the pH to 8.0 by addition of Et_3N, was added. This was followed by addition of a warm (45 °C) solution of **4** (5 g, 5.75 mmol) in 2-methoxyethanol (15 mL). The remainder of the initiator was added portion wise to the reaction mixture over 1 h and the reaction monitored to completion. The reaction was quenched with $NaHCO_3$ and worked up in EtOAc and the product deprotected in MeOH, as previously described, to afford **3**.

Method III. Example of a Reaction Using a Basic Phase-Transfer Agent. ACVA (1.13 g, 4 mmol) was suspended in cold solvent (10 mL) and the pH adjusted to between 7 and 8 by addition of cold PTA solution (5.75 mmol). A portion (2/3) of the above mixture was added, under N_2, to a refluxing mixture of NaH_2PO_2 (3.05 g, 28.75 mmol) in the solvent (50 mL). A warm (45 mL) solution of **4** (5 g, 5.75 mmol) in the solvent (15 mL) was added to the refluxing mixture. The remainder of the initiator mixture was added portionwise over 1 h and the reaction monitored to completion. The reaction was quenched with $NaHCO_3$ and worked up in EtOAc and the product deprotected in MeOH, as previously described, to afford **3**.

4″-*O*-(1-propionoxy)thionocarbonylerythromycin B (6). Compound **4** (20 g, 0.023 mol) was dissolved in 1-propanol (200 mL) and cooled to −10 °C. KtBuO (2.58 g 0.023 mol) was added and the mixture stirred and allowed to warm to room temperature. Stirring was continued until the reaction was complete (ca. 1 h). Solvent was removed in vacuo, and the product was purified by silica gel chromatography (acetone/hexane 1:1) to afford **7** (12.1 g, 61%). Compound **7** (5 g, 5.8 mmol) was deprotected in MeOH as described above and the product crystallized in CH_3CN with a molecule of methanol to afford **6** (4.3 g, 90%): HRMS (FTMS-ESI(+)) calcd for $C_{41}H_{74}NO_{13}S$ (M^+) 820.4875, found 820.4876. Anal. Calcd For $C_{41}H_{73}NO_{13}S \cdot CH_3OH \cdot 0.5CH_3CN$: C, 59.18; H, 9.07; N, 2.41; S, 3.67. Found: C, 59.12; H, 9.04; N, 2.42; S, 3.73. The structure was confirmed by X-ray crystallography.

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Supporting Information Available: A full list of ^1H NMR and ^{13}C NMR listings with assignments, MS fragments, and X-ray crystallographic data for 4″-*O*-(1-propionoxy)thionocarbonyl erythromycin B. This material is available free of charge via the Internet at http://pubs.acs.org.

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