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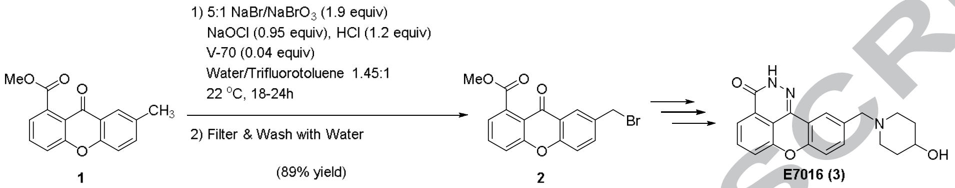

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A Green Bromination Process for Synthesis of a Novel Drug Candidate

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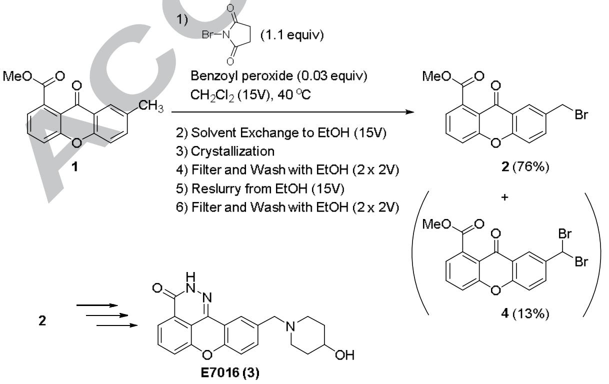
ABSTRACT

A bromination process has been developed using a salt-based brominating reagent and a non-chlorinated solvent system. The process affords enhanced selectivity and enables product isolation by simple filtration of the reaction mixture, resulting in a substantially reduced waste stream.

Introduction

E7016 (**3**) is an inhibitor of poly (ADP-ribose) polymerase currently being investigated clinically as a potential anticancer therapy. A key intermediate in the synthesis of E7016 is benzylic bromide **2**, which is prepared via bromination of methylxanthene **1**. The original process for bromination of **1** employed *N*-Bromosuccinimide in dichloromethane with benzoyl peroxide as radical initiator. This process was employed on kilogram scale to deliver an early batch of E7016. During the implementation of this first-generation process, several problems were identified that would require resolution to enable a robust process for future synthesis of E7016.



Scheme 1. Bromination en route to E7016

Results and Discussion

The first-generation bromination process transferred to our department had several challenges. First, the reaction generated substantial quanitities (>15%) of dibromide **4** in addition to the desired monobromide (**2**) requiring multiple reslurries to upgrade the purity of **2**. Second, the radical reaction was prone to stalling, requiring repeated fresh charges of benzoyl peroxide and *N*-bromosuccinimide to re-initiate the reaction. Finally, the reaction used a halogenated solvent (dichloromethane) and required multiple chases with ethanol to accomplish solvent exchange resulting in a significant organic waste stream.

At the outset of our studies, we were attracted to a salt-based bromination reagent reported by Adimurthy et al.[1] This reagent (5:1 $NaBr/NaBrO_3$), the precursor of liquid bromine via cold process manufacture, liberates bromine upon acidification. The ratio of NaBr to $NaBrO_3$ can also be adjusted using NaOCl via a redox process according to:

$$5\ NaBr + NaBrO_3 + 3\ NaOCl \rightarrow 4\ NaBr + 2\ NaBrO_3 + 3\ NaCl$$

This allows one to achieve an optimal mixture for specific bromination reactions.[2] We recognized that this reagent would afford superior atom economy[3] compared to *N*-bromosuccinimide, which generates a substantial organic by-product in succinimide. Further, since this reagent was salt-based, it could be eliminated in the aqueous waste stream.

Our initial experiments (Table 1) focused on the optimization of this reagent for the bromination of **1** in the current dichloromethane (10 mL/g) reaction solvent. After some

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experimentation, it was found that the 5:1 mixture of NaBr/$NaBrO_3$ derived from the bromine cold manufacturing process was useful directly in this process (entries 2-8), using NaOCl and HCl as co-reactants as described by Adimurthy et al.[2] Importantly, the reaction was confirmed to be photoinitiated by two experiments conducted in the dark to prevent photoinitiation (entries 6 & 7). Adapting the process to a production environment with closed reactors and thus limited ambient light would require chemical initiation. Since it was desirable to conduct the reaction at near-ambient temperatures, we introduced the initiator V-70 to good effect (entry 8).[4]

Table 1. – Evaluation of NaBr/$NaBrO_3$ Brominating Reagent as Substitute for *N*-Bromosuccinimide in Dichloromethane

Entry	Equiv NaBr/NaBr O_3 (ratio)	Equiv NaOCl	Equiv HCl	T (°C)	Other	Product Distribution at End of Reaction (%)		
						1	2	4
1	1.1 equiv NaBr/$NaBrO_3$ (2:1)	0	1.1	22	-	16	64	12
2	2.0 equiv. NaBr/$NaBrO_3$ (5:1)	1.0	2.2	22	-	1	74	5
3	1.8 eq. NaBr/$NaBrO_3$ (5:1),	0.9	2.0	22	-	5	84	11
4	1.8 eq. NaBr/$NaBrO_3$	0.9	1.1	22	-	6	82	12
5	1.8 eq. NaBr/$NaBrO_3$ (5:1)	0.9	1.1	0	-	5	87	8
6	1.8 eq. NaBr/$NaBrO_3$ (5:1)	0.9	1.1	22	In the dark	100	0	0
7	1.8 eq. NaBr/$NaBrO_3$ (5:1)	0.9	1.1	40	In the dark	100	0	0
8	1.8 eq. NaBr/$NaBrO_3$ (5:1)	0.9	1.1	22	In the dark + V-70 initiator (0.1equiv)	10	80	10

While these new reaction conditions afforded reliable bromination without need of *N*-bromosuccinimide, the problems of significant dibromination, chlorinated solvent use, and an organic solvent-intensive workup remained. We theorized that one cause of dibromination might be the solubility of the initial monobromide product **2** in the reaction solvent. Exposure of **2** to additional brominating agent within the reaction matrix would presumably give rise to **4**. With this in mind, we assessed the solubilities of the starting material **1** and monobromide **2** in several solvents in an effort to identify a solvent(s) that might solubilize **2** to a lesser extent than **1** and potentially have less environmental impact than dichloromethane.

Table 2 shows absolute and relative solubility data for **1** and **2** in three solvents that also afforded reasonable extent of reaction for the bromination. The cost of each solvent from a commmon chemical supplier are also listed.[5]

Table 2. – Solubility Data for **1** and **2** in Several Organic Solvents Compatible with NaBr/$NaBrO_3$ Bromination Reaction

Compound	Solubility Data		
	DCM ($45/L)	Chlorobenzene ($80/L)	α,α,α-Trifluorotoluene ($51/L)
Starting Material **1**	125 mg/mL	83 mg/mL	**19 mg/mL**
Monobromide **2**	104 mg/mL	47 mg/mL	**5 mg/mL**
Relative Solubility ½	1.20 : 1	1.76 : 1	**3.8 : 1**

As can be seen from Table 2, α,α,α-trifluorotoluene (TFT, a.k.a. trifluoromethylbenzene) afforded preferential solubility for starting material **1** over the desired monobrominated product **2**, while reducing overall solubility. It was hoped that reaction conditions could be found where **2** might crystallize directly from the reaction mixture, reducing the formation of dibromide **4** and providing a simple isolation procedure for **2** that would mitigate additional solvent use for extraction and solvent exchange. Additionally, α,α,α-trifluorotoluene has received attention as a green solvent alternative to halogenated hydrocarbons such as dichloromethane.[6]

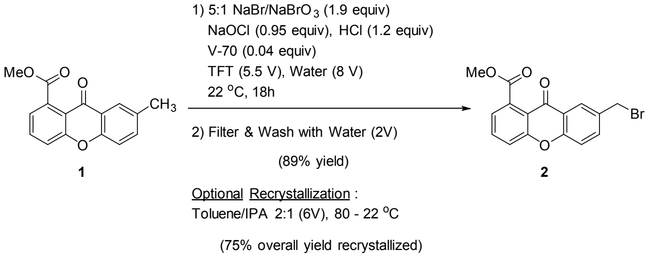
Adapting the optimal reaction conditions in dichloromethane to this new solvent revealed that, at reasonable volumes of α,α,α-trifluorotoluene with water as co-solvent, reactivity could be maintained while simultaneously controlling levels of dibromide **4**. Furthermore, the desired monobrominated product **2** could be isolated directly by filtration of the reaction mixture, thus eliminating the need for additional solvent for extractions and chases.

Table 3. – Optimization of NaBr/$NaBrO_3$ Reaction Conditions in α,α,α-Trifluorotoluene (TFT) and Water Solvent System[a]

Entry	Equiv NaBr/$NaBrO_3$ (ratio)	Equiv NaOCl	Equiv HCl	T (°C)	Volumes TFT (mL/g)	Volumes Water (mL/g)	Product Distribution at End of Reaction (%)		
							1	2	4
1	1.8 eq. NaBr/$NaBrO_3$ (5:1)	1.0	1.1	22	10	4	2	83	12
2	1.8 eq. NaBr/$NaBrO_3$ (5:1)	1.0	1.1	22	5	4[b]	6	88	6
3	1.8 eq. NaBr/$NaBrO_3$ (5:1)	1.0	1.1	22	5.5	8	4	88	8

[a] All reactions employed 0.1 equiv of V-70 initiator.
[b] Reaction mixture was viscous and difficult to stir using only 4 volumes of water.

Scheme 2 and Table 4 show the results of a kilo-scale demonstration of this new bromination process. The monobrominated product **2** was isolated directly from the reaction mixture with 93% HPLC purity, which is suitable for use directly in the downstream process as subsequent steps effectively control levels of residual **1** and **4**. A simple recrystallization procedure provides higher purity material if desired.[7]



Scheme 2. Final Bromination Process

Table 4. Results of Kilo-scale Demonstration of New Bromination Process

Product Distribution at End of Reaction (%)			Isolated Yield	Intial Isolated Purity (HPLC Area%)	Overall Yield Post-Recrystallization	Recrystallized Purity (HPLC Area%)
Starting Material (1)	2	4				
6	**84**	**10**	**89%**	**93%** **Residual 1: 5%** **Residual 4: 2%**	**75% Yield**	**98%** **Residual 1: 1.5%** **Residual 4: 0.2%**

A comparison of waste generated by the original and new bromination procedures is presented in Table 5. The new bromination procedure affords a significant reduction in overall waste and a 83% reduction in organic waste.

Table 5. Waste Metrics for Original Bromination Procedure and New Bromination Procedure

Original Bromination Process (*N*-bromosuccinimide, dichloromethane)		New Bromination Process (NaBr/$NaBrO_3$ 5:1, NaOCl, HCl, Trifluorotoluene)	
Aqueous Waste (kg/kg **1**)	Organic Waste (kg/kg **1**)	Aqueous Waste (kg/kg **1**)	Organic Waste (kg/kg **1**)
2	39	16	6.5
Total: 41 kg waste/kg **1**		Total: 22.5 kg waste/kg **1** (45% reduction)	

In conclusion, we have developed and implemented a simple salt-based bromination process for preparation of **2** that affords good reaction performance and selectivity while minimizing waste production.

Acknowledgments

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References and notes

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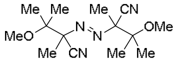
2. Adimurthy, S.; Ghosh, S.; Patolia, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. *Green Chem.* **2008**, *10*, 232.
3. Trost, B.M. *Angew. Chem. Int. Ed. Engl* **1995**. *34*, 259.
4. V-70 Initiator (2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile) was purchased from Wako Pure Chemicals Industry, Ltd. CAS# 15545-97-8.



5. Cost information from Sigma-Aldrich for anhydrous-grade solvent, 2-liter or 4-liter size.
6. Ogawa, A.; Curran, D. P.; *J. Org. Chem.***1997**, *62*, 450.
7. A representative laboratory-scale procedure is as follows: A 2-Liter jacketed reaction vessel was charged with sodium bromide (60.6 g, 0.59 mol, 1.6 equiv), sodium bromate (18g, 0.12 mol, 0.32 equiv), sodium hypochlorite solution (98 mL, 0.35 mol, 0.95 equiv), and water (800 mL) under a nitrogen atmosphere. The resulting mixture was allowed to stir at 20-25 °C for 20 mins. To this mixture was charged a slurry of methylxanthene **1** (100g, 0.37 mol) in trifluorotoluene (550 mL). To the resulting light yellow slurry was charged concentrated HCl (38 mL, 0.46 mol, 1.2 equiv) at such a rate as to maintain the internal temperature ≤ 25 °C. The reactor was then covered with aluminum foil to exclude light. V-70 initiator (4.6g, 0.015 mol, 0.044 equiv) was added and the mixture was allowed to stir for 20-24 hours until HPLC analysis indicated the reaction was complete (≤ 5% of **1** remaining). The mixture was filtered through a sintered glass funnel. The resulting wet cake was washed with water (800 mL) and dried under vacuum to afford bromide **2** (113g, 87% yield) as a white solid.
   The product could be recrystallized as follows: Crude **2** (113g) was suspended in toluene (452 mL) and isopropanol (226 mL). The resulting suspension was heated to 80 °C, then slowly cooled to 20 °C and held at 20 °C for 12 h. The resulting white solid was filtered and washed with 2:1 toluene/isopropanol (220 mL), then dried under vacuum to afford recrystallized **2** (96.17g, 85% recovery, overall yield 74%) as a white solid.