Fluorous Tagged *N*-Hydroxy Phthalimide for the Parallel Synthesis of *O*-Aryloxyamines

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The parallel synthesis of *O*-aryloxyamines remains an unfulfilled need in the field of medicinal chemistry and fragment-based approaches. To fill this gap a solution-phase two-step process based on (1) a copper-catalyzed cross-coupling of aryl boronic acids with a fluorous tagged *N*-hydroxyphthalimide, and (2) a supported aminolysis was designed and optimized using Taguchi's method. A library of *O*-aryloxyamines was synthesized in high yields with high purity and diversity.

Introduction

The biological[1] and pharmacological activities[2] of *O*-aryloxyamines or their oxime derivatives[3] have attracted much interest in medicinal chemistry.[4] In addition, chemoselective ligation strategies through oxime bond formation with oxyamines have received considerable attention in chemical biology,[5] fragment-based drug discovery,[6] drug targeting,[7] combinatorial,[8] dynamic[9] and iterative library synthesis.[10]

Despite their high potential, only a limited number of *O*-aryloxyamines are commercially available, and the synthesis of a corresponding library remains a challenge. To our knowledge, no parallel synthesis of *O*-aryloxyamines has been reported to date.

Traditionally, solid phase synthesis is privileged for parallel syntheses to avoid purification problems associated with solution-phase synthesis. However, the incompatibility of polymer-supported reagents with many reaction conditions as well as the difficulties associated with the characterization of polymer-bound intermediates and the monitoring of the reaction progress have limited the scope of its application.

A wide variety of solution-phase approaches that address these limitations while retaining the purification simplicity have emerged.[11] Among these, "light-fluorous synthesis"[12] is based on the addition of perfluoroalkyl groups as "phase tags" which facilitate purification steps using fluorous solid-phase extraction (F-SPE). Reactions can be carried out in homogeneous solution using common organic solvents, and their progress can be monitored by conventional analytical methods without tag removal. In addition, since fluorous tags exhibit high thermal and chemical stabilities the tagged compounds can be subjected to almost any chemical reaction.

The present paper demonstrates a successful application of fluorous tag technology to the parallel synthesis of *O*-aryloxyamines.

Results and Discussion

O-Aryloxyamine syntheses via nucleophilic aromatic substitution of electrophilic arenes with *N*-hydroxyl group donors[13] or via nitrogen transfer to an aryloxide[14] have been described, but these methods are limited in scope or use unstable reagents difficult to prepare. More recently Petrassi et al[15] described the copper-mediated cross-coupling of phenylboronic acids with *N*-hydroxyphthalimide followed by hydrazinolysis to access a larger diversity of *O*-aryloxyamines. The use of heterogeneous conditions and the formation of side-products make this two-step strategy of little practical use for parallel synthesis. Since we previously reported a supported *N*-hydroxyphthalimide reagent for the parallel synthesis of a wide diversity of *O*-alkyl hydroxylamines from aliphatic alcohols,[16a] we first attempted to extend it to arylboronic acids coupling for the parallel synthesis of *O*-aryl hydroxylamines. Different reaction conditions were screened with no success. A similar failure was observed when the cross-coupling was performed in solution between arylboronic acids and exo-*N*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide, an *N*-hydroxyimide previously reported for a ROMP-based *O*-alkyl hydroxylamine parallel synthesis.[17] This suggested that the use of *N*-hydroxyphthalimide in solution is mandatory for an efficient coupling reaction. With the goal of combining the versatility of solution phase synthesis with the purification facility of F-SPE, we envisaged a two step process using cross-coupling of aryl boronic acid with a fluorous-tagged *N*-hydroxyphthalimide reagent **1** followed by aminolysis of the so-formed *O*-aryl phthalimides **3** (Scheme 1).

The tagged reagent was obtained on a multigram scale from commercially available 2-perfluoroalkyl-1-iodoethane **5** and trimellitic anhydride via a five step convergent synthesis with a 44% overall yield (Scheme 2).

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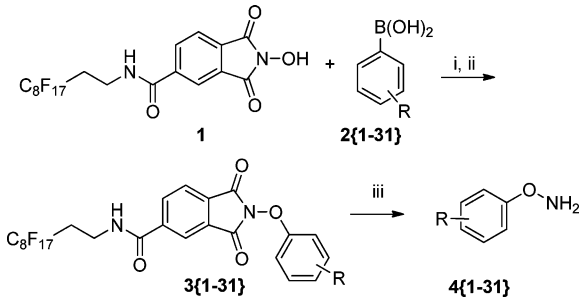
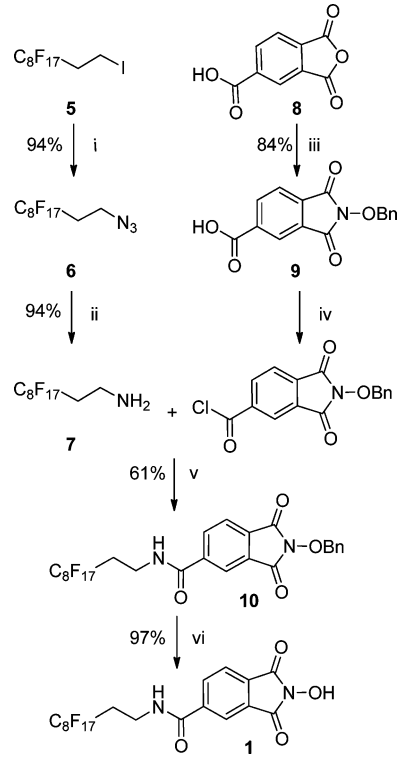
Scheme 1. Parallel Synthesis of *O*-aryloxyamines



Reaction conditions: (i) $Cu(OAc)_2$, Pyridine, O_2, benzotrifluoride (BTF), rt, 48 h; (ii) F-SPE; (iii) Aminomethylated Polystyrene resin from Novabiochem, $CHCl_3$/MeOH (9:1), rt, 24 h.

Scheme 2. Synthesis of the Fluorous-Tagged *N*-Hydroxyphthalimide Reagent **1**



Reaction conditions: (i) NaN_3, DMSO/water (50:1), rt, 90 h; (ii) 55 PSI H_2, Pd/C, Et_2O/MeOH (5:2), rt, 24 h; (iii) $BnONH_2 \cdot HCl$, Microwave, neat, 200 °C, 10 min; (iv) $SOCl_2$, DMF, 55 °C, 1 h; (v) **7**, DIPEA, rt, 18 h; (vi) 55 PSI H_2, Pd/C, Methylethyl ketone, rt, 24 h.

Among the reported conditions tested[18] for nucleophilic substitution of iodide **5** with sodium azide, the best results were obtained using a mixture of dimethyl sulfoxide (DMSO)/water as solvent.[19] The azide **6** was then reduced into the amine **7** by palladium catalyzed hydrogenation. Condensation of trimellitic anhydride **8** with *O*-benzyl hydroxylamine hydrochloride under microwave irradiation[16a] without any solvent led to the efficient formation of *O*-protected phthalimide **9**. Coupling of its acid chloride derivative with the amine **7** followed by palladium-catalyzed hydrogenolysis gave the fluorous-tagged *N*-hydroxyphthalimide **1**. The use of *O*-allyl protecting group for the *N*-hydroxyphthalimide moiety was also evaluated. However, difficulties encountered in removing the soluble palladium catalysts used for *O*-allyl cleavage prompted us to prefer the benzyl protection (see Supporting Information). Copper-mediated cross-coupling of phenylboronic acid **2.{1}** with this tagged reagent under Petrassi's conditions[15] occurred in moderate yields (40−60% yield) and prompted us to optimize this step. We suspected solubility problems but cannot exclude any other factor. To accelerate this approach we resorted to using Taguchi's method. This fractional factorial design optimization technique uses Taguchi-designed orthogonal arrays (OA), in which only a fraction of the combination of variables are considered to minimize the number of experiments while covering a wide range of operating conditions and maintaining all the information/data intact.[20] Following the selection of the proper OA, a statistical analysis of the experimental data by the analysis of variance (ANOVA) determines the influencing parameters, reveals their interactions, and quantifies their effect.[21]

Table 1. Considered Factors and Their Levels in the Design of Experiments

		level[b]			
	factor[a]	1	2	3	4
A	catalyst	$Cu(OAc)_2$	CuCl		
B	base	Pyr[c]	Et_3N	LutMy[c]	MetIm[c]
C	oxidant	Air	O_2	PNO[c]	TEMPO[c]
D	solvent	CH_2Cl_2	DCE[c]	THF	BTF[c]
E	*T* (°C)	20	55		
F	reaction time	48 h	96 h		

[a] Independent variable that may influence the response and which is expressed by the letters A−F. [b] A distinction within a parameter which is expressed by a number 1−4. [c] Abbreviations: DCE, 1,2 dichloroethane; LutMyc, lutidine with myristic acid; MetIm, *N*-methyl imidazole; PNO, pyridine *N*-oxide; Pyr, pyridine; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxide.

On the basis of the literature results on copper-mediated *N*-and *O*-arylations[22] we selected catalyst, base, oxidant, solvent, temperature, and reaction time as factors likely to affect the yield (A−F Table 1). Each of the studied factors has up to four levels (Table 1) and five interactions were considered (AB, AC, AD, AE, AF).

Consequently, a L32(2^{31}) OA was chosen and combined with parameters defined in Table 1 to plan the experimental conditions (Supporting Information, Table S2). The yield for each of the 32 reactions was determined by quantitative HPLC analysis of crude reaction media. From these results (Supporting Information, Table S2) and their ANOVA statistical analysis, it was possible to quantify the influence of each factor as well as their interactions (Supporting Information, Table S3).[21] The catalyst was found to be the dominant factor (63% contribution) followed by the base (15%) and the solvent (7%). The catalyst/base interaction was found to be the only statistically significant one (95% confidence level) among the 5 tested. Optimum conditions were obtained by combining levels with the best effect (Supporting Information, Figure S2) for these main factors. This simplified Taguchi method led us to perform the reaction in the presence of $Cu(OAc)_2$ and pyridine in BTF at 20 °C. BTF has been shown to possess the appropriate solvent properties for fluorous reagents[23] and to exhibit proper dioxygen solubilization.[24] A 4-fold excess of boronic acid was revealed to be necessary to ensure total consumption of hydroxyphthalimide **1** but resulted in an increased formation of diphenyl ether. The presence of this side-product can be explained by the competitive arylation of water

Table 2. Yields and Purities of *N*-Aryloxyphthalimides **3{1−31}** and *O*-Aryloxyamines **4{1−31}**[a]

R	3	% yield[b] (% purity)[c]	Lit.[d]	4	% yield[e] (% purity)[f]
		Ortho Substituted			
H	**3.{1}**	99(100)	90	**4.{1}**	93(93)
Me	**3.{2}**	90(100)	60	**4.{2}**	96(96)
CN	**3.{3}**	20(43)		**4.{3}**	0
CF_3	**3.{4}**	30(98)		**4.{4}**	91(91)
F	**3.{5}**	4(66)	0	**4.{5}**	0
		Para Substituted			
Me	**3.{6}**	96(100)		**4.{6}**	93(93)
OMe	**3.{7}**	51(55)	37	**4.{7}**	0
CN	**3.{8}**	76(95)	66	**4.{8}**	91(91)
CF_3	**3.{9}**	88(98)	65	**4.{9}**	92(92)
Cl	**3.{10}**	96(95)		**4.{10}**	93(93)
Br	**3.{11}**	94(100)	73	**4.{11}**	95(95)
I	**3.{12}**	92(98)	57	**4.{12}**	92(92)
CHO	**3.{13}**	76(86)	52	**4.{13}**	0[h]
$CH{=}CH_2$	**3.{14}**	89(97)	87	**4.{14}**	90(90)
Ph	**3.{15}**	97(83)		**4.{15}**	16(40)[f]
2-Thiophene	**3.{16}**	87(97)		**4.{16}**	0[g]
		Meta Substituted			
Me	**3.{17}**	95(100)		**4.{17}**	98(98)
OMe	**3.{18}**	88(99)	57	**4.{18}**	94(94)
CF_3	**3.{19}**	92(98)	87	**4.{19}**	94(94)
F	**3.{20}**	93(98)	65	**4.{20}**	96(96)
SMe	**3.{21}**	73(81)		**4.{21}**	82(82)
OCF_3	**3.{22}**	95(99)		**4.{22}**	96(96)
CO_2Me	**3.{23}**	87(93)		**4.{23}**	95(95)
Ph	**3.{24}**	98(99)		**4.{24}**	95(95)
OBn	**3.{25}**	93(96)		**4.{25}**	90(90)
OBn(2-Cl)	**3.{26}**	92(97)		**4.{26}**	91(91)
OBn(3,5-$(OMe)_2$)	**3.{27}**	93(96)		**4.{27}**	89(89)
$CONEt_2$	**3.{28}**	96(97)		**4.{28}**	96(96)
		Disubstituted			
3,5-F_2	**3.{29}**	89(100)	72	**4.{29}**	90(90)
3,5-$(OMe)_2$	**3.{30}**	98(99)		**4.{30}**	87(87)
		Fused			
1-naph	**3.{31}**	93(100)		**4. {31}**	0[g]

[a] See chapter 6 of Supporting Information for the procedure used. [b] Determined by gravimetry and taking into account the purity. [c] Determined by UHPLC/MS with UV detection at 220 nm. [d] Yields reported by Petrassi et al.[15] [e] Determined by gravimetry and taking into account the purity determined after derivatization into acetone oxime (see Supporting Information). [f] Purity determined by UHPLC/MS with UV detection at 220 nm after derivatization into acetone oxime derivatives. [g] Phenol derivative was the major product. [h] This product polymerizes.

released from the phenylboronic acid followed by coupling of the so-formed phenol with the phenylboronic acid in excess as previously reported. As the formation of this impurity could not be prevented despite the use of different anhydrous conditions,[25,26] the F-SPE elution protocol was adapted to solve this problem. The FluoroFlash SPE cartridges were first eluted with three successive fluorophobic solvent mixtures: (1) DMSO/H_2O (90:10) to remove all nonfluorous material including diphenyl ether; (2) MeOH/H_2O (70/30) to eliminate DMSO, and (3) cyclohexane to remove all apolar contaminants (e.g., silicon grease from BTF). The desired product was then eluted in high purity with acetone as fluorophilic solvent. We explored the scope and the limitations of the optimized conditions on a range of structurally diverse arylboronic acids **2{1−31}**. In agreement with Taguchi's predictions, most of the products were obtained in excellent isolated yields (Table 2), even higher than those previously described[15] on the same substrates with the classical procedure, and with high purity. The reaction proceeds smoothly with both electron-rich and electron-deficient arylboronic acids as well as in the presence of a wide range of functional groups. However, no coupling could be detected either with heterocyclic boronic acids, such as pyridine, furan or thiophene, or with phenylboronic acid bearing electron-withdrawing group (F, CF_3 or CN) in the ortho position (Table 2).

Aminolysis of *N*-phenyloxyphthalimide **3.{1}** with $MeNH_2$ solution (MeOH or $CHCl_3$/MeOH (80:20)) for 24 h at room temperature was quantitative. The so-formed *O*-phenyloxyamine **4.{1}** was purified by fluorous SPE and collected in the fluorophobic fraction (CH_3OH/H_2O (80:20)). However, its relative volatility resulted in a loss of material, a behavior which was noticed with a number of other *O*-aryloxyamines. As a result, we considered using a supported aminolysis in a volatile solvent to recover the *O*-aryloxyamines via a simple filtration. Several commercially available aminomethyl[27] and ethylenediamine branched resins[28] were tested in three solvent systems: MeOH, MeOH/$CHCl_3$ (90:10), and $CHCl_3$. The best results were obtained using the aminomethylated polystyrene resin from Novabiochem in $CHCl_3$/MeOH for 24 h at room temperature. The *O*-aryloxyamines **4.{1−31}** were reproducibly obtained in quantitative yield (based on chemset **3**) and high purity (Table 2). The latter was determined by liquid chromatography/mass spectrometry (LC/MS) analysis after conversion to their corresponding acetone oximes (handling of the free oxyamines is difficult because of their rapid reaction with any trace of carbonyl compounds).

Conclusion

In this study, we have described the first parallel synthesis of diverse *O*-aryloxyamines combining the use of a new fluorous-tagged *N*-hydroxyphthalimide reagent **1**, purification by reversed-phase fluorous SPE and finally a supported aminolysis. The Taguchi design of experiments was successfully applied for the optimization of the key copper-mediated reaction. The standardized Taguchi method was initially used to allow a minimum number of experiments. However, the interesting results gathered in this research suggest that this method, besides saving time, gives reliable results and allows the systematic study of synthesis parameters and of their possible interactions.

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Supporting Information Available. Details of experimental procedures and analytical data were given. It includes ^1H NMR, ^{13}C NMR, ^{19}F NMR spectra, IR and MS spectra. Details for Taguchi's Design of Experiments are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) 70 to 90% of this side product was obtained in the presence of molecular sieves activated at temperatures up to 540°C, or $MgSO_4$ activated at 200°C or using BTF dried over P_2O_5. The absence of a drying agent led to a much higher ratio of diphenylether.

(27) (1) ArgoPore-NH_2-HL from Argonaut (1.22 mmol/g, lot No. 01664); (2) ArgoGel-NH_2 from Argonaut (0.45 mmol/g, lot No. 01458); (3) Aminomethylated Polystyrene EHL from Novabiochem.

(28) Stratospheres PL-EDA (ethylenediamine) resin from Aldrich (100 mesh, 1% cross-linked lot No. 16513TI).

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