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Polymer-assisted solution-phase library synthesis of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids

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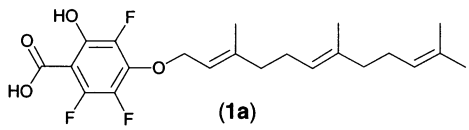
Abstract—The efficient synthesis of a small library of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids is described via the fluoride mediated alkylation of 5,6,8-trifluoro-7-hydroxy-2-methyl-benzo[1,3]dioxin-4-one with a collection of structurally diverse bromoalkanes. The use of ion-exchange resins during the reaction sequence enabled the preparation of the majority of the products in 82–98% purity without the need for chromatography.

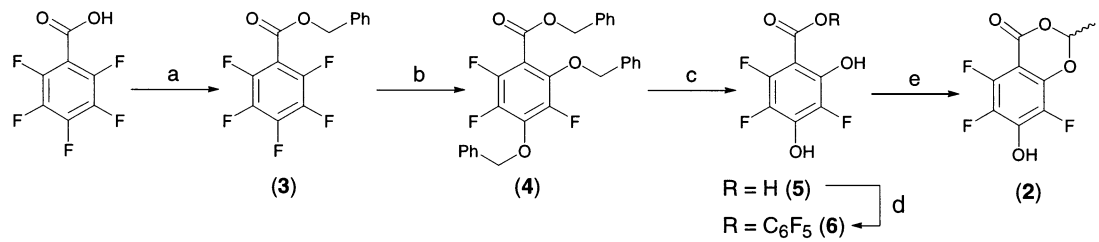
We have previously reported the synthesis of 4-farnesyloxy-2-hydroxy-3,5,6-trifluorobenzoic acid (**1a**) during a search for novel inhibitors of the enzyme farnesyl transferase (FTase) an important target for cancer therapy.[1] Similarly, we have reported the solid-phase synthesis of a library of 1-alkoxy-3-hydroxy-4-nitro-2,5,6-trifluorobenzenes via Mitsunobu alkylation of the corresponding phenol with a diverse collection of alcohols.[2] We required a rapid, efficient and general route to 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids (**1**) to provide a small library of compounds of sufficient purity for biological evaluation against FTase.



(**1a**)

Efficient methods for the alkylation of solid-phase-tethered alcohols and phenols are rarely reported.[3] The use of solid-phase bases such as conventional ion-exchange resins[4] and polymer supported organic bases,[5] however, has proved popular to promote alkylation. One advantage of this approach is that the alkylation reaction liberates the product from the resin, thus yielding pure product. Polymer-supported scavenging reagents have also been used extensively to provide clean, efficient reaction sequences.[6–8] In this paper we report the synthesis and alkylation of 5,6,8-trifluoro-7-hydroxy-2-methyl-benzo[1,3]dioxin-4-one (**2**) with a collection of structurally diverse bromoalkanes, followed by deprotection and purification using polymer-supported scavenging reagents to provide a library of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids (**1**).

The key intermediate protected *o*-hydroxybenzoic acid **2** was prepared from the pentafluorophenyl ester **6**, which was prepared by an improved route modified from that previously published (Scheme 1).[1] Pen-



Scheme 1. *Reagents and conditions*: (a) $PhCH_2Br$, Cs_2CO_3, DMF; (b) $PhCH_2OH$, KO^{t}Bu, THF; (c) H_2, Pd-C, MeOH-H_2O; (d) $C_6F_5OCOCF_3$, pyridine, CH_2Cl_2; (e) i. CH_3CHO, DABCO; ii. BioRad AG 50W X-4 H^+, MeOH.

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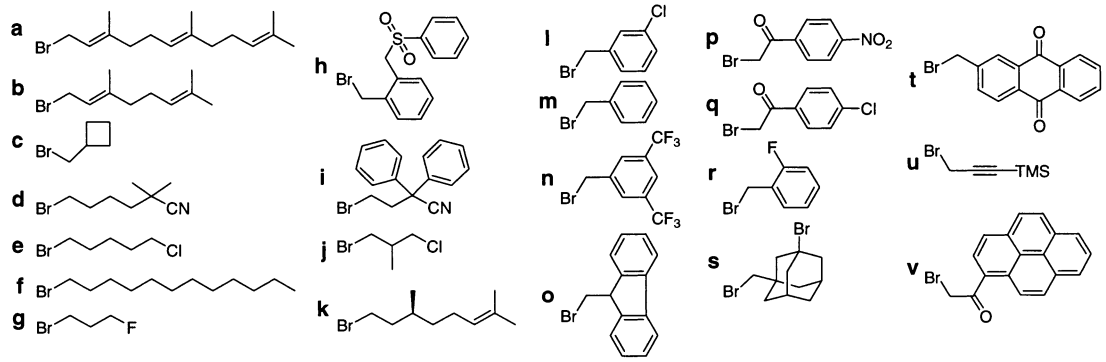


Figure 1. Structures of diverse alkyl bromides (**7**).

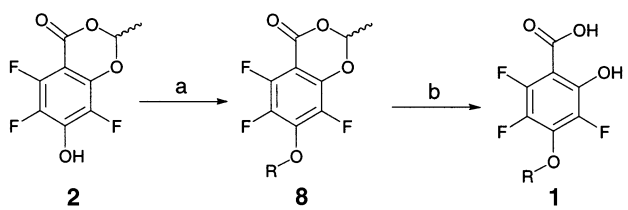
tafluorobenzoic acid was converted to the benzyl ester **3**, which was subjected to a double nucleophilic aromatic substitution with potassium benzylalkoxide to give the 2,4-substituted product (**4**) in 62% yield, accompanied by the 2,4,6-trisubstituted product (ca. 12%). Hydrogenolysis smoothly deprotected **4** to give the *o*-hydroxybenzoic acid derivative **5** in 91% yield. Conversion of acid **5** to the activated pentafluorophenyl ester **6** under standard conditions enabled conversion to the 1,3-benzodioxinone **2** by treatment with DABCO in neat acetaldehyde.[9] The resulting DABCO salt precipitated from the reaction mixture. The phenol **2** was liberated by passing a methanolic solution of the salt through a cation exchange column (BioRad AG 50W X-4 H^+ form), and was isolated in 45% yield, based on **6**.

Alkylation of phenol **2** with geranyl bromide using cesium carbonate as base gave the sodium salt of the product **1b** following deprotection in good yield (82%). However, as anticipated, the electron-poor phenoxide ion was unreactive towards simple alkyl bromides, thus a more general method was sought. Initial attempts to alkylate the phenoxide generated on solid-phase with either weakly basic Amberlite® IRA-68, strongly basic Amberlite® IRA-900,[4] or the polystyrene supported guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD)[5] met with failure.

The use of fluoride as a base for *O*-alkylation of phenols, including acidic phenols, e.g. 2-nitrophenol, has been reported.[10–13] Alkylation of phenol (**2**) was attempted with a selection of fluoride bases, i.e. CsF, KF on alumina, Et_4NF, n-Bu_4NF on alumina. The optimal conditions were found to be cesium fluoride (5 equiv.) as base, alkyl bromide (**7**) (3 equiv.), in DMF with vigorous stirring at 60°C.

A selection of 20 diverse bromoalkanes (**7c**–**v**, Fig. 1) was chosen from a list of commercially available chemicals using a 2D dissimilarity clustering program.[14] Alkylation of **2** under the optimal conditions with the majority of bromoalkanes (**7c**–**v**) proceeded smoothly to give the products **8** (Scheme 2). The DMF and volatile alkyl bromides were removed by evaporation. Unreacted phenol **2** was removed from the filtered reaction mixture by sequential treatment with (a) Amberlyst 15 acid resin in THF to protonate any unreacted cesium phenoxide ion and (b) Amberlyst A-21 basic resin to sequester the unreacted phenol **2**, leaving a mixture of the product **8** and remaining unreacted bromoalkane (**7c**–**v**). Deprotection was effected with aqueous sodium hydroxide (0.5 M) in dioxane (1:3) to give the *o*-hydroxybenzoic acid sodium salts, which were converted to the corresponding acids **1** by treatment with acidic Dowex 50WX2-200 resin in ethanol/water (1:1). The acids were sequestered from the crude mixture with basic Amberlyst A-21 and purified by repeated washing with THF, then released from the resin by treatment with 20% aq. formic acid in THF. The solvent was evaporated and the products analysed by LCMS, and ^1H and ^{19}F NMR spectroscopy. The crude yields, estimated purities and molecular masses found are summarised in Table 1.

The results show that for 11 of the 20 alkyl bromides (**7c**–**m**) chosen the desired product was formed with an isolable yield. In three cases the product (**1n**–**p**) was observed in the LCMS, but the concentration was judged to be insufficient for further purification. The failed reactions could be attributed to the presence of a β-ketone in the alkyl bromide (**7p,q,v**), poor solubility (**7s,t,v**), or reactivity towards the fluoride base (**7u**). In six of the cases the product (**1c,e,f,i**–**k**) was formed in >80% purity and 13–46% yield without the need for further purification. In five cases (**1d,g,h,l,m**) preparative TLC purification was required to provide sufficiently pure product, albeit in low yield. Products (**1c**–**m**) were assayed for activity versus farnesyl transferase and geranylgeranyl transferase I according to



Scheme 2. *Reagents and conditions*: (a) i. RBr (**7c**–**v**), CsF, DMF; ii. Amberlyst 15, THF; iii. Amberlyst A-21, THF; (b) i. aq. NaOH (0.5 M), dioxane; ii. Dowex 50WX2-200, H_2O, EtOH; iii. Amberlyst A-21, THF; iv. 20% formic acid, H_2O, THF.

Table 1.

Alkyl bromide (**7**)	Product (**1**)	Yield (%)	Purity (%)[a]	HPLC-ESMS data[c] calcd/found $[M-H]^-$
c	**c**	31	82	275/275
d	**d**	25	94[b] (60)	330/330
e	**e**	36	87	311/311
f	**f**	46	97	375/375
g	**g**	18	85[b] (59)	267/267
h	**h**	14	100[b] (71)	451/451
i	**i**	13	96	426/426
j	**j**	24	95	297/297
k	**k**	34	98	345/345
l	**l**	2	93[b] (20)	331/331
m	**m**	10	86[b] (57)	297/297
n	**n**	Nd	14	433/433
o	**o**	Nd	52	385/385
p	**p**	Nd	49	370/370
q–v	**q–v**	0	0	–

[a] Analysis by LCMS (C18 reverse phase Supelco Discovery 50×4.6 mm column; gradient elution 90–10% 0.1% aq. formic acid/methanol, 1.0 ml/min for 10 min) by area integration.
[b] Following purification by preparative TLC.
[c] Obtained using a Finnigan LCQ ion trap mass spectrometer.

published procedures.[15] None of the compounds displayed significant activity against the target enzymes.

In conclusion, we have prepared a library of diverse 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids (**1c**–**m**). The utility of fluoride as a base in alkylation reactions with poorly nucleophilic phenols has been demonstrated. Solid-phase reagents have been used throughout the synthetic route to provide the desired compounds in a rapid, efficient manner. Biological evaluation of the library has demonstrated the poor activity of this group of compounds against the target enzymes.

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