Carbon−Carbon Bond-Forming Methods on Solid Support. Utilization of Kenner's "Safety-Catch" Linker

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Intensive research efforts have focused on the combinatorial synthesis of biopolymers,[1] unnatural polymers,[2] and, most recently, organic compounds.[3] The successful construction of a combinatorial library of a class of compounds depends on the availability of general and high-yielding strategies for synthesizing the compounds on solid support.[4] The development of general strategies for the formation of carbon−carbon bonds is of particular importance for the construction of organic compound libraries. Here we report a general and high-yielding method for the solid-phase synthesis of substituted arylacetic acid derivatives **6** (Scheme 1) that represent an important class of cyclooxygenase inhibitors.[5] The key carbon−carbon bond-forming reactions in the synthesis sequence are enolate alkylation,[6] one of the most fundamental of carbon−carbon bond-forming methods,[7] and palladium-mediated Suzuki cross-coupling,[8] a method that is extensively employed in natural product synthesis and in medicinal chemistry.

Cyclooxygenase inhibitors that are built upon the phenylacetic acid core typically incorporate three elements of variability: an α-alkyl group, R^1; alkyl, aryl or heteroaryl substitution on the phenyl ring, R^2; and acid or amide functionality, X (Scheme 1). The appropriate choice of a linker to attach the phenylacetic acid to the solid support is central to the successful synthesis of these compounds. The linkage must be compatible with the basic enolate alkylation and Suzuki reaction conditions, yet at the end of the synthesis it must be labile for nucleophilic cleavage of the final product from the solid support. The seldom used acylsulfonamide linker that was developed by Kenner for peptide synthesis fulfills these requirements.[9] Under basic conditions, the acylsulfonamide ($pK_a \sim 2.5$) is deprotonated, preventing nucleophilic cleavage; however, once solid-support synthesis is complete, treatment with diazomethane results in the formation of the *N*-methylated derivative that is activated for nucleophilic displacement (vide infra).

The sulfonamide-derivatized support **1** (Scheme 1) can readily be prepared by treating aminomethylated resin with 4-carboxybenzenesulfonamide, *N,N*-diisopropylcarbodiimide, and 1-hydroxybenzotriazole.[10,11] Treatment of the sulfonamide resin **1** with the pentafluorophenyl active ester of 4-bromophenylacetic acid and 4-(dimethylamino)pyridine then provides the acylsulfonamide **2**.[12,13] The first step in the synthesis of the arylacetic acid derivatives is enolate alkylation to introduce the R^1 group. Treatment of the acylsulfonamide **2** with excess LDA (15 equiv) in THF at 0 °C results in rapid deprotonation to give the trianion.[14] Subsequent addition of activated alkyl halides, such as methyl iodide or benzyl bromide, or highly unactivated alkyl halides, such as isopropyl iodide, results in rapid and complete alkylation of the enolate dianion to provide **4**. It should be noted that, in contrast with ester[15] or carboximide[16] enolate alkylations, ketene formation is not observed, even with the unreactive alkylating agent isopropyl iodide, since ketene formation would require that the sulfonamide dianion be the leaving group.[17] In addition, minimal overalkylation is observed; the bisalkylated product was detected only for alkylation with methyl iodide and at a level of only 4% (Table 1, entry **6c**).[18] After the alkylation reaction is complete, the alkylated product is protected from cleavage under the basic reaction conditions since the acylsulfonamide remains deprotonated.[19]

The Suzuki reaction is a powerful carbon−carbon bond-forming method for the rapid introduction of diverse substituents onto an aromatic ring. The reaction conditions are mild, and a very large number of alkylborane coupling partners are accessible through the in situ hydroboration of olefins, while many arylboronic acid coupling partners are available commercially. On solid support, the Suzuki reaction of acylsulfonamide **4** is performed according to standard conditions using $Pd(PPh_3)_4$ as the catalyst, 2 M aqueous Na_2CO_3 as the base, and THF as the solvent at reflux for 24−40 h.[20,21] Deprotonation of the acylsulfonamide again prevents hydrolysis under the basic reaction conditions. Good conversion is observed both for alkyl-

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(4) For an overview of synthesis on solid supports: Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327−333.

(5) Synthesis studies directed toward this compound class have served as a useful test of carbon−carbon bond-forming methods.

(6) Limited studies on enolate alkylation on solid support have been performed: (a) Leznoff, C. C.; Worster, P. M.; McArthur, C. R. *Angew. Chem., Int. Ed. Engl.* **1978**, *18*, 221−222. (b) Kurth, M. J.; Schore, N. E.; Moon, H. *J. Org. Chem.* **1992**, *57*, 6088−6089.

(7) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. C., Ed.; Marcel Dekker: New York, 1979; Vol. 1.

(8) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749−1758.

(9) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636−637.

(10) Kenner prepared the sulfonamide resin by first treating sulfonic acid resin with chlorosulfonic acid followed by addition of ammonium hydroxide. We chose to build off of the aminomethyl resin because many different types of aminomethyl resins are readily available and because 4-carboxamide substitution of the benzenesulfonamide should result in a more activated derivative in the nucleophilic cleavage step (vide infra).

(11) The macroreticular form, rather than the gel form, of polystyrene cross-linked with 2% divinylbenzene was employed due to the reported greater site accessibility of the macroreticular resin under anionic reaction conditions: Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877−3881.

(12) In preliminary results, resin **1** can also be acylated with symmetric anhydrides and DMAP. The loading level is determined by *N*-methylation of the acylsulfonamide resin **2** followed by treatment with benzylamine to provide the *N*-benzylamide product (vide infra).

(13) The reaction conversion for coupling 4-carboxybenzenesulfonamide to the support to provide **1** can be monitored by the standard ninhydrin test. The reaction conversion for acylating sulfonamide **1** can again be monitored by the ninhydrin test since the sulfonamide **1** gives a pale red color, while acylsulfonamide **2** does not result in coloration of the beads or of the ninhydrin solution. Kaiser, E.; Colescot, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595−598.

(14) Treatment of sulfonamide **1** or acylsulfonamide resin **2** with LDA results in resin beads that are blue in color. Upon addition of alkylating agents to trianion **3**, the blue color is rapidly quenched.

(15) Rathke, M. W.; Woodbury, R. P.; Sullivan, D. F. *J. Org. Chem.* **1977**, *42*, 2038−2039.

(16) Evans, D. A.; Mathre, D. J.; Ennis, M. D. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(17) Treatment of the acylsulfonamide **2** with excess LDA (15 equiv) in THF for 2 h at 23 °C, followed by *N*-methylation and benzylamine treatment, results in a quantitative yield of the *N*-benzyl amide product.

(18) Whether or not alkylation of the carboxamide functionality occurs is inconsequential since the linker remains attached to the support after the nucleophilic cleavage step.

(19) The acylsulfonamide anion is a very poor nucleophile and is not alkylated under the reaction conditions. This was demonstrated by submitting alkylation product **4** (R^1 = Me) to the benzylamine cleavage conditions (vide infra) with no *N*-benzyl amide being produced.

(20) Forcing reaction conditions were employed to ensure complete reaction conversion.

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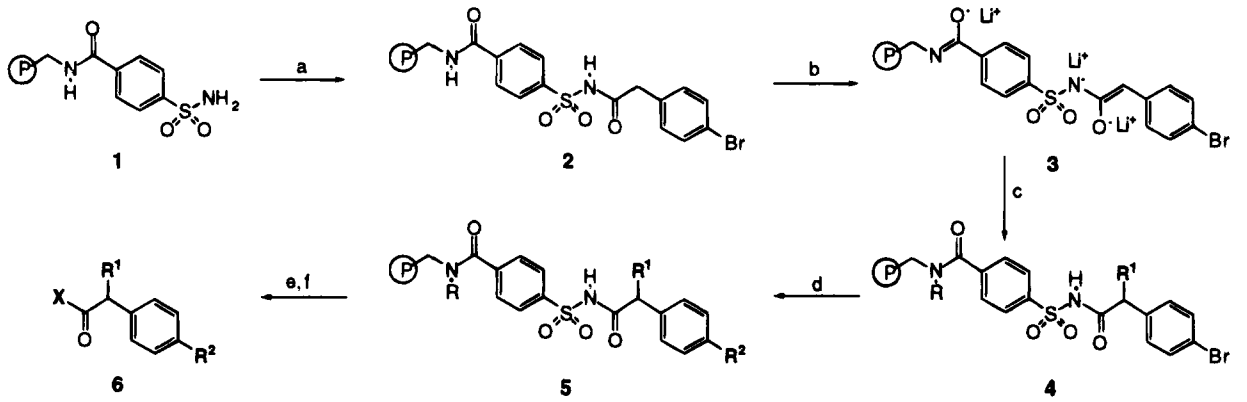
Scheme 1[a]



[a] Reaction Conditions: (a) pentafluorophenyl 4-bromophenylacetate, 4-(dimethylamino)pyridine; (b) LDA, THF, 0 °C; (c) alkyl halide, 0 °C; (d) alkyl-9-BBN or arylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, THF, 65 °C; (e) CH_2N_2; (f) HO^- or amine.

Table 1. Substituted Arylacetic Acid Derivatives **6** (Scheme 1)

entry	R^1	derivative R^2	nucleophile	yield (%)[a,b]
6a	H	$(Me)_2CHCH_2$	H_2O	100
6b	Me	$(Me)_2CHCH_2$	H_2O	96
6c	Me	$(Me)_2CHCH_2$	$BnNH_2$	96
6d	Bn	$(Me)_2CHCH_2$	$BnNH_2$	98
6e	Et	$(Me)_2CHCH_2$	$BnNH_2$	92
6f	*i*-Pr	$(Me)_2CHCH_2$	$BnNH_2$	91
6g	Me	$(Me)_2CHCH_2$	piperidine	96
6h	Me	$(Me)_2CHCH_2$	aniline	0[c]
6i	H	Ph	H_2O	93
6j	Me	Ph	$BnNH_2$	95
6k	Me	4-F_3CPh	$BnNH_2$	87
6l	Me	4-MeOPh	$BnNH_2$	88
6l	Me	2,4-Cl_2Ph	$BnNH_2$	88

[a] Yields are based on the loading level of support bound starting material **2** (see ref 12). [b] The purity of all compounds was confirmed by ^1H and ^{13}C NMR analysis as well as by elemental analysis, except for the therapeutic agents Ibufenac (**6a**), Ibuprofen (**6b**), and Felbinac (**6i**). [c] No cleavage of material off of the resin was observed when aniline was employed as the nucleophile.

9-BBN derivatives (Table 1, entries **6a-h**) and for arylboronic acids that are electron-poor or electron-rich as well as ortho-substituted (Table 1 entries **6i−m**). It should be noted that protodehalogenation was not observed in any of the Suzuki coupling reactions.

The final step in the synthesis is nucleophile-mediated cleavage of the material from the support. Acylsulfonamide activation is accomplished by first rinsing the acylsulfonamide **5** with 5% trifluoroacetic acid in THF to ensure complete protonation, followed by treatment with CH_2N_2 in Et_2O. Nucleophilic cleavage of the material from the support is then accomplished by treatment with either hydroxide at room temperature or an amine in THF or dioxane at elevated temperatures.[20] As shown in Table 1, hydroxide cleanly provides the carboxylic acids Ibufenac **6a**, Ibuprofen **6b**, and Felbinac **6i**, whereas nucleophilic amines such as benzylamine and piperidine provide high yields of the amide derivatives (entries **6c−g** and **6j−l**). However, attempted cleavage of the material from the resin with aniline did not provide any anilide product and defines the level of reactivity of the activated acylsulfonamide linkage (entry **6h**).

The reaction scope in the enolate alkylation and in the Suzuki-mediated reactions, as well as other palladium-mediated processes, is under further investigation,[22] as is the utility of more activated sulfonamide linkers. The application of these solid-phase synthesis strategies to a number of combinatorial synthesis targets is also in progress and will be reported in due course.

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Supplementary Material Available: Experimental details, including analytical data for all compounds described in this work (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) The only other solvent that was investigated was dimethoxyethane. When dimethoxyethane was employed, precipitation of Pd(0) greatly complicated subsequent synthesis steps (Pd(0) efficiently catalyzes the decomposition of CH_2N_2).

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