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Convenient synthesis of functionalized terphenyls

A. A. Greenfield,* J. A. Butera and C. E. Caufield

Chemical Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543-8000, USA

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Abstract—A convenient synthetic methodology amenable for rapid synthesis of differentially functionalized terphenyls is described. Orthogonality requirements for the incorporation of phenoxy acetic acid and carboxamide function have been satisfied by utilization of hydroxyethoxy group as a precursor of the acid. Highly efficient and universal procedures have been developed for acid and amide formation.

Acid-containing terphenyls (**8**) have recently been found to be potentially useful modulators of insulin receptor function with possible utility in the treatment of hyperglycemia.[1–4] Their elaboration into orally active antihyperglycemic agents targeted for type II diabetes required fine-tuning of physico-chemical parameters to optimize pharmacokinetic properties of the compounds. A rapid matrix synthetic approach was implemented to build a representative set of compounds for structure–activity relationship analysis. An efficient and universal synthetic methodology (Scheme 1) was designed and developed to produce nearly 150 compounds for biological evaluation.

The regioselective synthesis of oligoaryls has been well documented (Ref. 5 and references cited therein) due to the importance of these substances as intermediates in different fields of study. To be amenable for a rapid matrix synthesis, the optimal choice of components/conditions was important in order to: (a) minimize the total number of steps within the scheme, and (b) create a universal synthetic methodology applicable for every combination of reaction components (the set of boronic acids and amines used in the synthesis is shown in Fig. 1). Incorporation of an oxyacetic acid synthon prior to the cross coupling and construction of the carboxamide satisfied a conceptual requirement of rapid matrix approach with the latest possible divergence. The details of the synthesis are described in Scheme 1.

The prerequisite ethyl-2-iodo-6-bromo-4-hydroxybenzoate (**2**) was conveniently prepared from ethyl-4-hydroxybenzoate (**1**) in high yield using known protocols.[6] As a sequel to earlier works,[5,7,8] we intended to use iterative aryl–aryl bond formation using a Suzuki Pd-coupling procedure. Since both symmetrically and nonsymmetrically arylated intermediates were targeted, an appropriate coupling protocol should provide access to both key intermediates **4** and **5**. Preliminary studies showed that when halogenated phenol (**2**) was subjected to Suzuki arylation conditions, the symmetrical product was formed; thus precluding divergence to unsymmetrical terphenyl template. Protection of the phenol became an imperative. In lieu of a traditional protection–deprotection sequence, we explored the possibility of incorporation of hydroxyethoxy function as both a protecting group and a precursor of the required oxyacetic group. Obviously, this approach could only be successful if an efficient conversion of alcohol into the acid could be implemented. Introduction of hydroxyethoxy function went uneventfully using an excess of ethyleneglycol and standard Mitsunobu conditions affording the product (**3**) in nearly quantitative yield. After extensive experimentation of cross-coupling conditions we found that the catalytic system containing [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$–DPPF)–K_2CO_3 in dioxane/water (5–10:1) at slightly elevated temperatures afforded almost quantitative conversion. Selectivities of 2–4:1 of monoarylated (**4**) versus bisarylated (**5**) intermediates, comparable with previous results[5] have been routinely achieved in all cases. Isolated yields of 60–70% were obtained after normal phase HPLC on silica column. A second arylation under similar conditions furnished even higher yields (70–90%) of differentiated core (**6**).

Keywords: Suzuki reaction; terphenyl compounds; tetrapropylammonium perruthenate oxidation.

* Corresponding author. Tel.: +1-732-274-4044; e-mail: greenfa@wyeth.com

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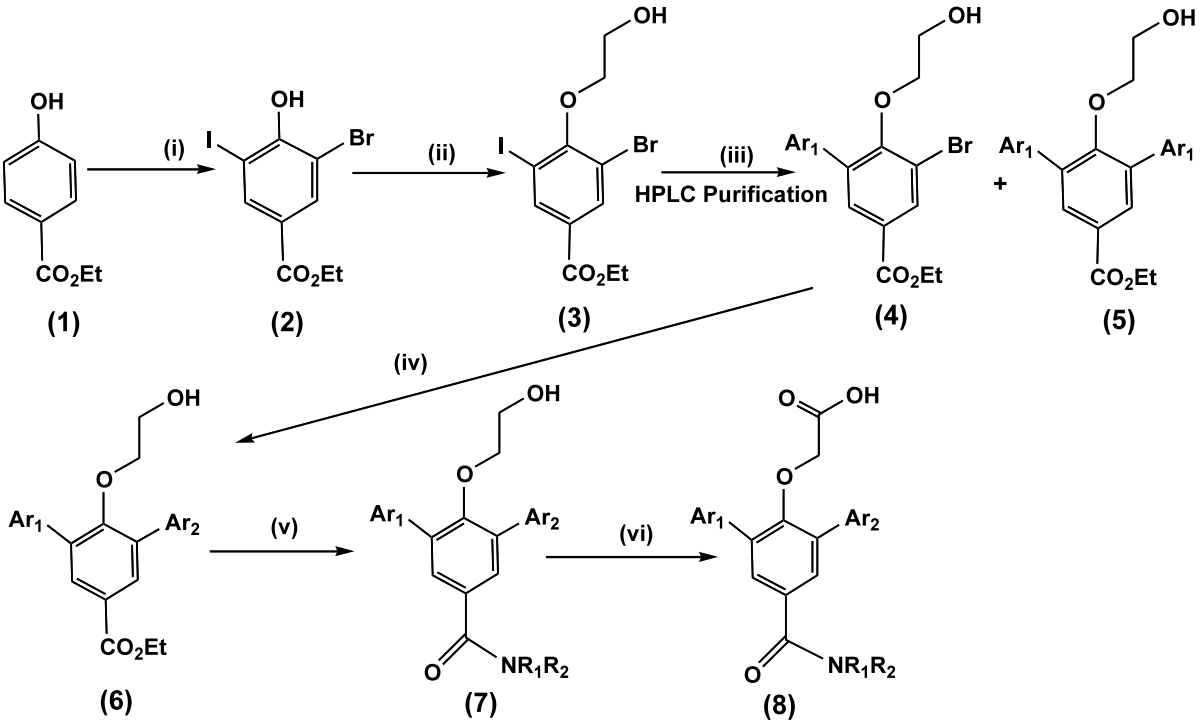
Symmetrical intermediates (**5**) were converted into corresponding final products using the same synthetic methodology.

The synthesis of amides (**7**) was accomplished using an excess of lithiated amines generated with *n*-BuLi (adapted and optimized from Ref. 9 at −20 to 0°C). The procedure proved to be successful even with problematic bromophenethyl amine and pyridylethyl amine. Moreover, incomplete conversions (possibly due to variable amounts of water in the reagents, for example) in some cases could be increased by addition of excess *n*-BuLi directly into reaction mixture. The minimal stoichiometry required extra equivalents of metallated amine for deprotonation of the alcohol function and amide formed in the case of primary amines (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) NBS, HBF_4, >90%; I_2, K_2CO_3, THF, >95%; (ii) PPh_3, DEAD, $HOCH_2CH_2OH$, >95%; (iii) $Ar_1B(OH)_2$, $PdCl_2$–DPPF, K_2CO_3, dioxane–water, 60–80°C, 60–70%; (iv) $Ar_2B(OH)_2$, $PdCl_2$–DPPF–K_2CO_3, dioxane–water, 60–80°C, 70–90%; (v) NHR_1R_2, *n*-BuLi, THF, −40°C to rt, 50–90%; (vi) TPAP, NMMO, CH_3CN, rt, 30–70%.

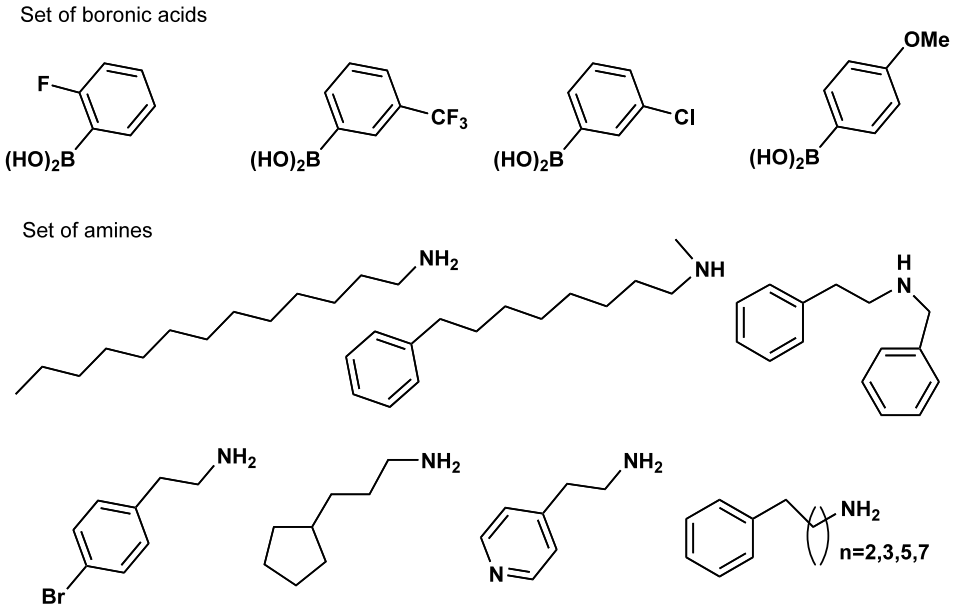


Figure 1.

Design and optimization of a selective and efficient oxidation methodology turned out to be rather challenging. Two successful approaches were explored: (a) CrO_3–MeCN system that provided sufficient conversion in the majority of cases, and (b) tetrapropylammonium perruthenate (TPAP)–*N*-methyl morpholine *N*-oxide (NMMO) traditionally used for selective alcohol–aldehyde conversion,[10,11] which we found to be extremely useful for alcohol–acid transformation. Due to better reproducibility, universal nature and facile isolation, the latter system was adopted. Adequate yields of target acids (**8**) were obtained when performing the oxidations in acetonitrile at ambient conditions and prolonged reaction times.

All intermediates and products synthesized in the course of this study have been isolated, purified and fully characterized. Comprehensive characterization data are available.[12]

In summary, we have established a convenient and potentially universal synthetic methodology amenable for a rapid synthesis of a series of highly functionalized and diversified terphenyls. Utilization of a hydroxyethoxy function serving as both protecting group and a precursor of oxyacetic fragment allowed us to minimize the overall number of synthetic steps. A powerful, yet synthetically simple procedure of conversion of alcohols into acids based on catalytic tetrapropylammonium perruthenate oxidation allowed us to use a uniform protocol for all target compounds and may serve as a useful expansion of this efficient methodology. The biological effects of these compounds will be reported elsewhere.

The general procedures are presented below.

Arylation. To a stirred solution of K_2CO_3 (3 mmol, 1.5 ml of 2 M solution) were added 10–15 ml of dioxane, 1 mmol of substrate (**3**) and 1.1–1.2 mmol of aryl boronic acid. The reaction flask was purged with nitrogen and 1–3 mol% of $PdCl_2$(DPPF) was added to the mixture. After stirring at room temperature for 0.5–1 h the temperature was raised to 50–60°C. The progress of the reaction was monitored by TLC. After typical work-up (dilution with water and acid or base followed by extraction) and evaporation of solvents the residue was placed onto flash column (eluent ethyl acetate–hexane) and quickly eluted to remove Pd residue. Typical conversions >95%, ratio monoaryl:bisaryl = 2-4:1.

Amidation. To a stirred cooled (below −20°C) solution of ester (**4**) or (**5**) (1 mmol) in 5–10 ml THF was added solution of an appropriate lithiated amine (see Fig. 1) in THF (below 0°C). Ideally, 2 equiv. is required for secondary amines and 3 equiv. for primary amines. The progress of the reaction was monitored by TLC. The reaction is instantaneous at room temperature, yet to avoid any complications it is recommended to mix the reagents at low temperature (−40°C) and allow the mixture to warm up. An excess of metallated amine is usually required to offset extra amounts of water. After completion the reaction mixture was quenched with water, treated with acid or base followed by extraction with ethyl acetate and evaporation of solvents. The crude material was purified by flash chromatography (eluent ethyl acetate–hexane). Typical conversions >95%, yield >80%.

Oxidation. To a stirred at room temperature solution of alcohol (**7**) (1 mmol) in 5–10 ml MeCN was added *N*-methylmorpholine-*N*-oxide (2 equiv., 2 mmol) and tetrapropylammonium perruthenate (10 mol%). The progress of the reaction was monitored by TLC. After completion the mixture was quenched with water or 2N HCl. Excess of sodium bisulphite is added and the mixture stirred for 10 min. After typical work-up (dilution with water and acid or base followed by extraction) and evaporation of solvents the residue was purified by flash chromatography (eluent ethyl acetate–methanol) or preparative thin layer chromatography. Typical conversions >95%, yields were in a range 30–70%.

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