

# Synthesis and cross-coupling reactions of solid-supported alkylzinc reagents

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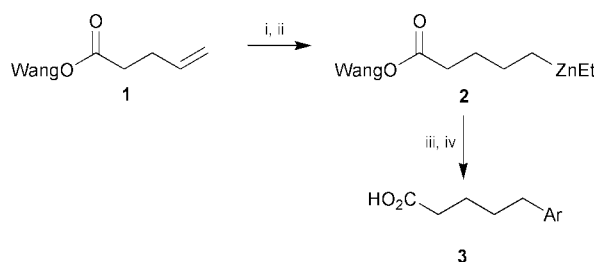
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Hydroboration of Wang-supported pent-4-enoic acid **1**, followed by transmetallation with Et<sub>2</sub>Zn, gives a solid-supported zinc reagent, **2**, which undergoes palladium-catalysed coupling with aryl iodides, to give the corresponding 5-arylpentanoic acids **3** in moderate to good yields, after cleavage from the resin using TFA.

Solid phase synthesis has developed into one of the main methods used in the construction of libraries of compounds in the search for biological activity. While a vast amount is known about the formation of carbon–heteroatom bonds on solid phase, the area of carbon–carbon bond formation has been less well-developed.<sup>1</sup> More specifically, the application of organometallic chemistry to carbon–carbon bond formation in solid phase synthesis has not been extensively investigated. There are examples of reaction of solid supported electrophiles with solution phase organometallic reagents, for example stannanes<sup>2</sup> and organozinc halides,<sup>3</sup> and this approach offers the advantage of being able to use a large excess of the organometallic reagent to ensure high conversion of the solid-supported electrophile. However, this approach has the dual disadvantages that each electrophile has to be loaded separately onto solid support, and also that the limited number of ‘off-the-shelf’ organometallic reagents means that most would need to be prepared separately. This clearly militates against the use of this chemistry in real library synthesis. By contrast, the large number of readily available electrophiles means that the preparation of solid-supported organometallic reagents has the potential to be much more generally applicable.

The preparation of solid-supported organometallic reagents was originally limited to the lithiation of cross-linked polystyrene, and this approach is widely used for the synthesis of modified polystyrene resins.<sup>4</sup> The use of solid-supported stannanes has been reported,<sup>5</sup> but these reagents are only appropriate for the transfer of unsaturated functionality. More recently, both aryl Grignard reagents<sup>6</sup> and aryl zincates<sup>7</sup> have been prepared from iodobenzoic acid derivatives supported on Wang resin. There is clearly a great need for the development of methods for the preparation of solid-supported alkylmetal derivatives, and the well-established functional group tolerance of alkylzinc reagents suggested that these might be good candidates.<sup>8,9</sup>

Organozinc reagents have most often been prepared by the heterogeneous reaction of alkyl iodides with metallic zinc, a process which is clearly not applicable to solid phase. A very attractive alternative is the overall conversion of an alkene into a dialkylzinc compound by initial hydroboration with diethylborane, followed by transmetallation with diethylzinc.<sup>10</sup> We have therefore prepared Wang-supported pent-4-enoic acid **1** (using 3 equivalents of pent-4-enoic acid relative to Wang resin). This material was subsequently treated with an equivalent of Et<sub>2</sub>BH in THF, and after washing, an excess of Et<sub>2</sub>Zn was added at 0 °C. Subsequent reaction with iodobenzene under palladium catalysis,<sup>†</sup> followed by cleavage from the resin using TFA,<sup>‡</sup> gave 5-phenylpentanoic acid **3a** (78%, based on resin loading of pent-4-enoic acid as determined by cleavage using TFA–CH<sub>2</sub>Cl<sub>2</sub> from a sample of the resin **1**), Scheme 1. A brief survey of the applicability of the process established that other



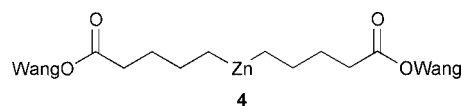
**Scheme 1** Reagents and conditions: i, Et<sub>2</sub>BH (1 equiv.), 5 °C, 30 min; ii, Et<sub>2</sub>Zn (10 equiv.), 0 °C, 30 min; iii, ArI (2 equiv.), Pd<sub>2</sub>(dba)<sub>3</sub> (2.5 mol.%), P(*o*-tol)<sub>3</sub> (10 mol.%), room temp., 16 h; iv, TFA, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 1 h.

**Table 1** Preparation of 5-aryl valeric acids

Ar-I	Product	Ar	Yield (%)
Ph-I	<b>3a</b>	Ph	78
4-MeC <sub>6</sub> H <sub>4</sub> -I	<b>3b</b>	4-MeC <sub>6</sub> H <sub>4</sub>	42
4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -I	<b>3c</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	58
3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -I	<b>3d</b>	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	44
2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -I	<b>3e</b>	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	42
1-Naphthyl-I	<b>3f</b>	1-Naphthyl	49

substituted aromatic iodides are also appropriate coupling partners (Table 1).

The usual product of zinc–boron exchange reactions is the symmetrical dialkylzinc species **4**,<sup>10</sup> towards which the equilib-



rium is shifted by removal of the triethylborane by distillation, although it is likely that the ethylalkylzinc species **2** is also formed in the presence of an excess of diethylzinc. On solid phase, the distinction between these two species is not important, since the ethylbenzene arising from coupling of the ethyl group in **2** with the electrophile is removed during the washing process after the coupling reaction and before the cleavage with trifluoroacetic acid.

This demonstration that simple functionalised alkylzinc reagents can be prepared on solid-support opens the possibility of the use of such reagents in library synthesis.

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## Notes and references

<sup>†</sup> Wang pent-4-enoate resin (500 mg, 0.55 meq) was allowed to swell with dry (distilled) THF (5 cm<sup>3</sup>) under N<sub>2</sub> in dry glassware. This mass of resin typically absorbed 3.8 cm<sup>3</sup> of THF. The excess solvent was decanted *via* a syringe, and the resin washed with THF (2 × 5 cm<sup>3</sup>). THF (2 cm<sup>3</sup>) was added, and the reaction cooled in ice–water before addition of diethylborane (80 μl, 0.56 mmol), prepared from triethylborane and borane–dimethyl sulfide complex. After 30 min the solvent was decanted, and the resin washed with THF (5 cm<sup>3</sup>). THF (2 cm<sup>3</sup>) was added and the suspension cooled to 0 °C, followed by the addition of Et<sub>2</sub>Zn (400–500 μl, 4–5 mmol).

After 30 min the solvent was decanted, and the resin washed with THF ( $2 \times 5 \text{ cm}^3$ ). THF ( $5 \text{ cm}^3$ ) was added, followed by  $\text{Pd}_2\text{dba}_3$  and  $\text{P}(o\text{-tolyl})_3$  (1:4 molar ratio 20–25  $\mu\text{mol}$  Pd) and the electrophile (1.1 mmol). The reaction was allowed to proceed overnight at rt (20–22 °C). The resin was poured into a sintered-funnel, drained in air, and washed thoroughly with THF until the washings ran clear. The resin was then treated with acetic acid–THF (50:50,  $50 \text{ cm}^3$ , 30 min), washed with THF ( $3 \times 20 \text{ cm}^3$ ) and then with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 20 \text{ cm}^3$ ).

‡ The resin was placed in a sintered-funnel and washed with dry (distilled)  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10 \text{ cm}^3$ ). The funnel was covered with aluminium foil, a mixture of  $\text{CH}_2\text{Cl}_2$  ( $1.5 \text{ cm}^3$ ) and TFA ( $5 \text{ cm}^3$ ) was added and the mixture allowed to stand for 1 h. The solvent was drained into a flask under  $\text{N}_2$ , and the resin washed with dry  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20 \text{ cm}^3$ ). The solvent(s) were evaporated to give the crude products as oils, from which the products crystallised upon standing. All products were recrystallised from petroleum ethers or petroleum ether– $\text{CHCl}_3$  systems.

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