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Palladium-catalysed α-arylation of esters and amides under microwave conditions

Emilie Bentz, Mark G. Moloney* and Susan M. Westaway

The Department of Chemistry, Central Research Laboratory, The University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
Department of Medicinal Chemistry, Neurology and GI CEDD, GlaxoSmithKline Research Ltd, New Frontiers Science Park, Third Ave, Harlow, Essex, CM19 5AW, UK

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Abstract—A rapid and convenient approach for the α-arylation of esters and amides using Reformatsky reagents under a microwave accelerated reaction protocol has been established.

The nucleophilic character coupled with low basicity and ease of preparation of Reformatsky reagents has resulted in their renewed interest as enolate sources. For example, they have been found to be effective in conjugate addition reactions with reactive enones, and more recently as nucleophilic partners in ligand coupling reactions with aryl halides mediated by palladium, chemistry extensively developed by Hartwig,[1–4] Buchwald[5–11] and others.[12,13] This latter reaction affords α-arylated esters and amides, a structural type which has hitherto been directly accessed by ligand coupling reactions making use of aryllead(IV) intermediates.[14] In view of the importance of this recently established Pd-mediated approach, it was of interest to us to examine the application of well-precedented microwave technology in combination with readily accessible Pd(0) catalysts to this reaction;[15,16] success would significantly simplify the existing protocol. The application of microwave acceleration to a variety of palladium-catalysed processes was demonstrated some time ago[17–20] and has been recently extended.[21–23] We report here the results of this investigation, detailing the efficiency and scope of a simple alternative procedure.

The required Reformatsky reagent was readily prepared by microwave irradiation of *tert*-butyl bromoacetate or dibenzyl bromoacetamide[24] with zinc in THF for 5 min at 100 °C; addition of this Reformatsky reagent to the coupling partner, an aryl bromide and the relevant catalyst/ligand in THF was followed by further irradiation for 5–10 min at 120 °C, and the reaction worked-up and the product obtained by chromatography[25] (Scheme 1). In this way, a number of substituted aryl bromides were converted to the corresponding arylacetic esters or amides (Table 1), generally in good yield and with short reaction times. However, some substrates with active hydrogens or reactive functions, such as ketones, alcohols and amines, were unsuitable, returning starting material or by-products, and in some cases isolation of the product was problematic due to difficulties removing phosphine residues. The requirement for microwave irradiation in these reactions was indicated by a control experiment (ethyl *p*-bromobenzoate, *tert*-butyl bromoacetate, Pd(0)(PPh$_3$)$_4$, THF, 70 °C, 18 h) but with no irradiation, which gave a mixture consisting mostly of unreacted starting material (58%) with only a small amount of the desired product (6%). Anhydrous THF proved to be the most effective solvent for the reaction, and DMF, DME, and CH$_3$CN all returned unreacted starting ethyl *p*-bromobenzoate.

The generality of this procedure was then examined; interestingly we found that the Reformatsky reagent derived from *tert*-butyl bromopropionate was unreactive with ethyl *p*-bromobenzoate under the microwave conditions, and dibenzyl bromopropionamide gave only a 5% yield of the expected product; thus, substitution at the α-position on the Reformatsky reagent was tolerated poorly. Noteworthy also is that the reaction proceeds

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Keywords: Arylation; Reformatsky; Catalysis; Microwave.

* Corresponding author. Tel.: +44 01865 275656; fax: +44 0186 5275674; e-mail: mark.moloney@chem.ox.ac.uk

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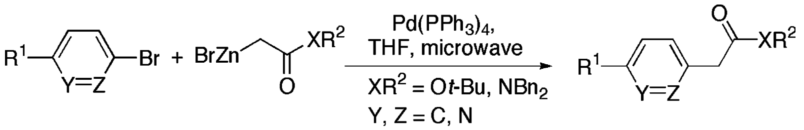

Scheme 1.

Table 1. Yields for coupling of Reformatsky reagents and aryl bromides according to Scheme 1

R^1	Y	Z	XR^2	Yield[a] (%)
EtO_2C	C	C	O*t*-Bu	98
	C	C	NBn_2	83
NC	C	C	O*t*-Bu	54
	C	C	NBn_2	53
O_2N	C	C	O*t*-Bu	68
	C	C	NBn_2	51
F_3C	C	C	O*t*-Bu	58
	C	C	NBn_2	84
t-Bu	C	C	O*t*-Bu	18
	C	C	NBn_2	78
H	C	N	O*t*-Bu	90[b]
	C	N	NBn_2	73
H	N	C	O*t*-Bu	52[c]
	N	C	NBn_2	21
O_2N	C	N	O*t*-Bu	53[c]
	C	N	NBn_2	36
F_3C	C	N	O*t*-Bu	36[c]
	C	N	NBn_2	38

[a] Isolated yield, except where otherwise indicated.

[b] Isolated as the carboxylic acid.

[c] Not isolated pure (contains Ph_3P residues).

most readily with $Pd(0)(PPh_3)_4$ as catalyst; other palladium catalysts ($Pd(OAc)_2$, $PdCl_2$ and Pd_2dba_3) and ligands (dppf, dppe, BINAP, PCy_3, and $P(o\text{-Tol})_3$) gave mixtures, containing ratios of starting material to product typically in the range 2:1 at best to 7:1 in the worst case; for the reaction catalysed by Pd_2dba_3/dppf/1-heptene,[26,27] more favourable ratios of 1:3 to 1:5 in favour of product were obtained, and in this case isolation of the desired product could be achieved in 54% yield.

We have shown that microwave accelerated reactions leading to α-arylation of ester and amide enolates using readily available $Pd(0)(PPh_3)_4$ catalyst is possible, and although the scope of these reactions is currently limited, microwave acceleration is likely to permit further enhancements of these useful coupling reactions.

Acknowledgements

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25. Typical procedure: *Step 1*. Preparation of the Reformatsky reagent: To a suspension of zinc (50 mg, 0.8 mmol) in THF (0.7 mL) was added a few crystals of iodine, followed by *tert*-butyl bromoacetate (59 μL, 0.4 mmol). The mixture was placed in a Personal Chemistry Emrys^{TM} Optimizer EXP microwave reactor and irradiated for 5 min to achieve a temperature of 100 °C. *Step 2*. Conjugate

addition reaction: To a solution of ethyl bromobenzoate (33 μL, 0.2 mmol) in THF (0.8 mL) was added a solution of the Reformatsky reagent in THF previously prepared (it is important not to add excess zinc reagent), followed by Pd(PPh_3)$_4$ (24 mg, 0.2 mmol). The mixture was replaced into the microwave reactor for 5 min to achieve a temperature of 120 °C. The reaction mixture was quenched with a saturated solution of ammonium chloride (3 mL) and extracted with EtOAc (4 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography to afford the desired product.

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