# Improved Palladium-Catalysed Synthesis of α-Benzyl-β-keto Esters

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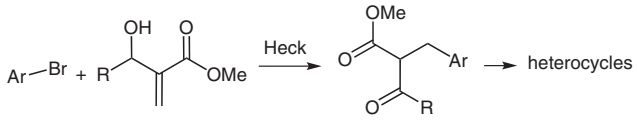
*Received 28 January 2010*

**Abstract:** This paper describes the development of an imporved protocol for the synthesis of α-benzyl-β-keto esters from aryl bromides via Heck reaction. The use of this protocol to synthesise a variety of diverse α-benzyl-β-keto esters for use in the preparation of new pharmaceutical agents is demonstrated.

**Key words:** palladium, Heck reaction, arylation, Baylis–Hillman, α-benzyl-β-keto ester

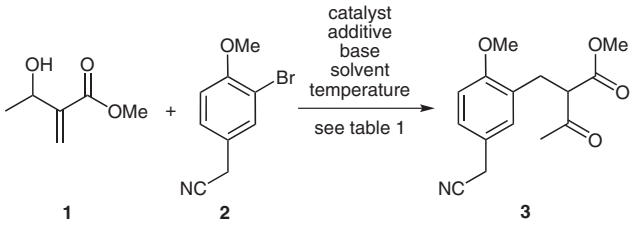
Palladium catalysis is a well-established tool for organic synthesis with a wide variety of applications. This includes the synthesis of new pharmaceutical agents as it allows for the efficient synthesis of carbon–carbon and carbon–heteroatom bonds.[1] The Heck reaction is one of the most commonly used palladium-catalysed transformations and this methodology has been used to solve a range of synthetic challenges.[2] We were focused on using Heck methodology to construct a range of structurally diverse α-benzyl-β-keto esters from aryl bromides (Scheme 1).[3] We envisioned that the use of this methodology would allow for the rapid synthesis of a range of structurally diverse α-benzyl-β-keto esters that could be subsequently converted into heterocyclic molecules, such as pyrazoles or pyrimidines,[4] for use in the preparation of pharmaceutically active compounds.




**Scheme 1**

The use of a Heck reaction for the synthesis of α-benzyl-β-keto esters has been previously reported[3a] and therefore we initially investigated the reaction between methyl 3-hydroxy-2-methylenebutanoate (**1**) and 2-(3-bromo-4-methoxyphenyl)acetonitrile (**2**, Scheme 2) using these conditions. However, in our hands the previously described protocol gave none of the desired product and only unreacted starting material was observed. We concluded that the presence of the *ortho*-methoxy substituent in the starting material could be responsible for the lack of reactivity in this case. Therefore, a range of catalyst systems were screened to try and discover conditions that gave a good conversion of starting material into product to for this reaction. Since 2-(3-bromo-4-methoxyphenyl)acetonitrile (**2**) appears to be a demanding substrate for this type of Heck reaction we anticipated that any conditions that were successful for this substrate would subsequently be applicable to a range of aryl bromides.

Our initial screen for an improved catalytic system focused on using homogeneous reaction conditions. In order to simplify the process we decided try a range of palladium catalysts whilst keeping the base (*N*-methyldicyclohexylamine, 1.5 equiv), additive [tetrabutylammonium chloride (TBAC), 10 mol%], and solvent (dimethylacetamide, 0.1 M) constant. The parallel screen of different palladium complexes showed 10 mol% Pd(dbpf)$Cl_2$ to be the only catalyst to give an acceptable conversion of starting material into product by HPLC (Table 1). All other catalysts gave either no or poor conversion. Further parallel experiments were then completed to optimise the reaction conditions using Pd(dbpf)$Cl_2$. It was found that increasing the amount of TBAC present in the reaction mixture from 10 mol% to 20 mol% gave an increased conversion of starting material into product. Changing the base used in the reaction had a negative effect on the overall conversion but increasing the loading of *N*-methyldicyclohexylamine gave complete conversion of starting material into product. Inceasing the reaction temperature from 80 °C to 100 °C also gave complete conversion of starting material into product provided the reaction was completed in a closed tube.[5] Solvent screening then indicated DMF to be optimum for this reaction. Finally, it was established that the catalyst loading could be reduced from 10 mol% to 2.5 mol% without reducing the conversion of starting material into product (Table 1).




**Scheme 2**

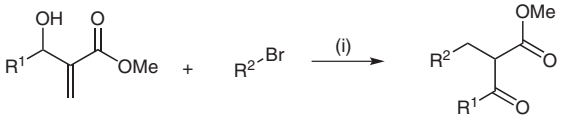
*SYNLETT* 2010, No. 11, pp 1688–1690
Advanced online publication: 15.06.2010
DOI: 10.1055/s-0030-1258095; Art ID: D02610ST

**Table 1**

| Entry | Catalyst (loading, mol%) | Additive (loading, mol%) | Base (loading, equiv) | Solvent | Temp (°C) | Concn (M) | Time (h) | Ratio product/**2**[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (2) | TBAB (100) | $NaHCO_3$ (2.5) | THF | 70 | 0.3 | 18 | 0:100 |
| 2 | $Pd(dbpf)Cl_2$ (10) | TBAC (10) | $NMeCy_2$ (1.5) | DMA | 80 | 0.1 | 18 | 50:50 |
| 3 | $Pd(dbpf)Cl_2$ (10) | TBAC (20) | $NMeCy_2$ (1.5) | DMA | 80 | 0.1 | 18 | 94:6 |
| 4 | $Pd(dbpf)Cl_2$ (10) | TBAC (20) | $NMeCy_2$ (3) | DMA | 80 | 0.1 | 18 | 100:0 |
| 5 | $Pd(dbpf)Cl_2$ (10) | TBAC (10) | $NMeCy_2$ (1.5) | DMA | 100[b] | 0.1 | 18 | 100:0 |
| 6 | $Pd(dbpf)Cl_2$ (2.5) | TBAC (20) | $NMeCy_2$ (3) | DMF | 100[b] | 0.3 | 18 | 100:0[c] |

[a] Ratio determined by HPLC of reaction mixture.
[b] Reaction completed in a closed tube.
[c] Isolated yield 92%.

Our attention then turned to investigating whether these optimised conditions could be applied to the Heck reaction between methyl 3-hydroxy-2-methylenebutanoate (**1**) and a range of aryl bromides containing electron-donating or -withdrawing substituents (Scheme 3). Pleasingly, all the substrates underwent efficient Heck reaction with **1**. To extend the methodology further, 3-bromopyridine and 3-bromothiophene were subsequently reacted with adduct **1** and again we were delighted to obtain good yield of the desired 1,3-dicarbonyl compounds **6f** and **6g** (Table 2).[6]




**1** $R^1$ = Me
**4** $R^1$ = Ph
**5** $R^1$ = 2-furyl

**6a–j**

**Scheme 3** *Reagents and conditions:* (i) $Pd(dbpf)Cl_2$ (2.5 mol%), *N*-methyldicyclohexylamine (3 equiv), TBAC (20 mol%), DMF, 100 °C (closed tube).

**Table 2 Synthesis of Compounds 6a–j**

| Entry | $R^1$ | $R^2$ | Product | Isolated yield (%) |
|---|---|---|---|---|
| 1 | Me | 4-$O_2NC_6H_4$ | **6a** | 53 |
| 2 | Me | 2-$MeOC_6H_4$ | **6b** | 85 |
| 3 | Me | 4-$MeC_6H_4$ | **6c** | 79 |
| 4 | Me | 3-$MeO_2CC_6H_4$ | **6d** | 99 |
| 5 | Me | 3-F-5-$CNC_6H_3$ | **6e** | 56 |
| 6 | Me | 3-pyridyl | **6f** | 56 |
| 7 | Me | 3-thiophene | **6g** | 67 |
| 8 | Ph | 2-$MeOC_6H_4$ | **6h** | 60 |
| 9 | Ph | 3-$MeO_2CC_6H_4$ | **6i** | 65 |
| 10 | 2-furyl | 2-$MeOC_6H_4$ | **6j** | 75 |

As the catalytic system had worked well for the arylation of **1** with a range of aryl/heteroaryl bromides we decided to investigate if it could be applied to the arylation of other Baylis–Hilman adducts. Thus, 2-[hydroxyl(phenyl)methyl]acrylate (**4**)[7] was successfully arylated with both 1-bromo-2-methoxybenzene and methyl-3-bromobenzoate to give the Heck products **6h** and **6i**, respectively, in good yield (Table 2). Similarly, the furanyl Baylis–Hilman adduct **5**[7] underwent Heck reaction with 2-methoxybenzene to yield the desired 1,3-dicarbonyl intermediate **6j** in good yield (Table 2).

In conclusion, we have developed an optimised protocol for the efficient synthesis of α-benzyl-β-keto esters from commercially available aryl bromides. We have demonstrated that this protocol works for a range of aryl and heteroaryl bromides, as well as a number of Baylis–Hillman adducts, to yield a diverse range of α-benzyl-β-keto esters. As these compounds represent key intermediates for synthesis of heterocyclic molecules this optimised protocol is ripe for application in the preparation of new pharmaceuticals.

## Acknowledgment

The authors thank Tom McInally (AstraZeneca), Dr. Steve Christie (Loughborough University), Professor Neil R. Thomas (University of Nottingham) and Professor Joe Sweeney (University of Reading) for their interest in this research and help with the preparation of this manuscript.

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(5) The reaction was completed in a closed tube with a bursting disc fitted in the top of the tube. The reaction was completed behind a blast screen and these important safety measures should be implemented when completing this reaction particularly when scaling up the procedure.
(6) **Typical Procedure for Heck Reaction**
1-Bromo-2-methoxybenzene (0.958 mL, 7.75 mmol), methyl 3-hydroxy-2-methylenebutyrate (0.942 ml, 7.75 mmol) and *N*-methyldicyclohexylamine (4.98 mL, 23.26 mmol) were added to a suspension of $Pd(dbpf)Cl_2$ (0.126 g, 0.19 mmol) and TBAC (0.431 g, 1.55 mmol) in DMF (10 ml) under nitrogen. The resulting suspension was stirred at 100 °C in a closed tube for 18 h (see ref. 5 for safety measures). The solution was diluted with EtOAc (50 mL) and extracted with $H_2O$ (50 mL) and brine (2 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was diluted with MeCN (30 mL) and loaded on to a 70 g SCX cartridge. The product was washed through with MeCN (100 mL) and the filtrate evaporated to give methyl 2-(2-methoxybenzyl)-3-oxo-butanoate (1.558 g, 85%) as an orange oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.20 (ddd, *J* = 8.9, 7.6, 2.1 Hz, 1 H, CH), 7.11 (dd, *J* = 6.8, 3.0 Hz, 1 H, CH) 6.87–6.82 (m, 2 H, CH), 3.92 (dd, *J* = 8.4, 7.2 Hz, 1 H, CH), 3.83 (s, 3 H, $CH_3$), 3.67 (s, 3 H, $CH_3$), 3.19 (dd, *J* = 13.9, 7.2 Hz, 1 H, $CH_2$), 3.10 (dd, *J* = 13.9, 8.2 Hz, 1 H, $CH_2$), 2.18 (s, 3 H, $CH_3$). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 203.1, 169.9, 157.3, 130.8, 128.1, 126.2, 120.5, 110.2, 59.0, 55.2, 52.2, 29.5, 29.4. HRMS (TOF-LCMS): *m/z* calcd for $C_{13}H_{17}O_4$ $[M + H]^+$: 237.1121; found: 237.1122.
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