

Palladium catalyzed Heck reaction of arenediazonium tetrafluoroborate salts with Baylis–Hillman adducts: production of α -benzyl- β -keto esters

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Abstract—A novel experimental procedure to obtain α -benzyl- β -keto esters from the Heck reaction between arenediazonium tetrafluoroborate salts and Baylis–Hillman (BH) adducts in the presence of Pd(OAc)₂ as catalyst is described. The methodology is simple, straightforward and the use of arenediazonium salts as opposed to conventional arylhalides/triflates over the usual Heck reaction is highlighted.

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The Baylis–Hillman reaction^{1,2} is a useful pathway for C–C formation. Recently there has been a growing interest to study its scope in terms of accommodating cyclic and substituted starting components and performing its asymmetric version, which is reflected in an increasing number of reports.³ Moreover, the resulted Baylis–Hillman (BH) adducts **1** have found a huge application as a versatile building block to generate either bioactive heterocyclic compounds such as 2-ethyl-2,3-dihydrobenzofuran carboxylic acid⁴ **2**, oxazolidin-2-ones⁵ **3**, 3,4-disubstituted 2,5-dihydrofuran(dihydropirrole)⁶ **4** and substituted dihydroisoquinolin-1(2*H*)-ones⁷ **5**, or useful synthetic intermediates⁸ (Fig. 1).

What makes BH adducts so attractive is the presence of three functionalities in the same molecular backbone, disposed in a unique manner, an ester group, an α,β -unsaturated moiety and an allylic alcohol.

The first Heck reaction using BH adducts and their acetates as the olefin source was published by Kumareswaran et al.⁹ The reaction was performed with iodobenzene in DMF for 3 h, under inert atmosphere in the presence of Pd(OAc)₂ as catalyst to afford either α -benzyl- β -keto esters or phenyl substituted α' -acetoxy- α,β -unsaturated

esters. These result prompted the use of this adducts as substrate for Heck and related reactions and several reports have appeared recently in the literature.¹⁰

Lately, the use of arenediazonium salts in palladium catalyzed C–C bond formation, as opposed to conventional aryl halides/triflates, has found an increasing application in the synthetic arena.¹¹ The process scores over the conventional Heck reaction on several counts, short reaction times, superior reactivity of the diazonium nucleofuge and in some cases the use of aqueous medium.¹²

With all these considerations in mind and following our interest in BH adducts as a suitable platform for the generation of heterocyclic compounds we proposed a new experimental procedure for rapid access to α -benzyl- β -keto esters by the Heck reaction.

The starting BH adducts **6a–f** were synthesized from methyl acrylate and the corresponding aliphatic or aromatic aldehyde in the presence of DABCO, under ultrasonic conditions.¹³ Arenediazonium tetrafluoroborate salt derivatives **7** were obtained following the standard procedure^{11a} from the respective aromatic amines, HCl NaNO₂ and sodium tetrafluoroborate. To extend the scope of our synthetic protocol, structurally diverse BH adducts and arenediazonium tetrafluoroborate salts with either electron donors (ED) or electron withdrawing (EW) groups attached to the arene moiety were used.

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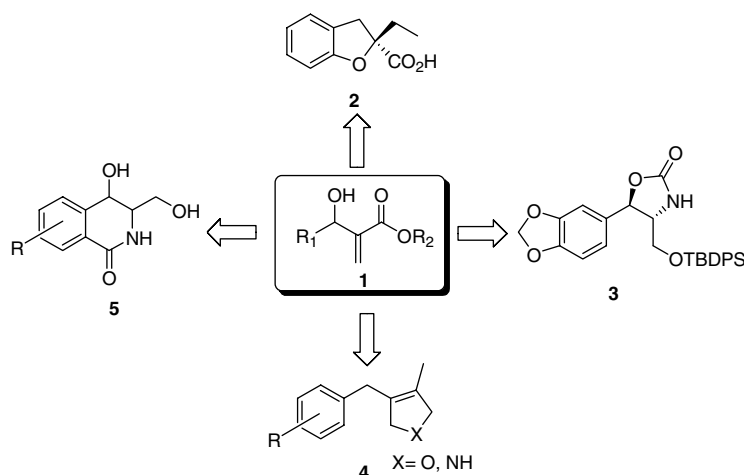


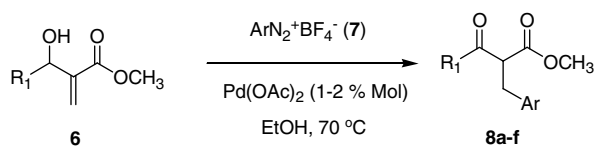
Figure 1. Baylis–Hillman adducts used as substrates for the total synthesis.

Combination of these reactants provides the expected α -benzyl- β -keto esters **8a–f** (Scheme 1).

The reaction is conveniently performed under aerobic conditions by mixing the two components in ethanol and stirring the mixture at 75 °C between 30 and 45 min as monitored by the evolution of nitrogen and the presence of Pd(0) with catalytic amounts of Pd(OAc)₂ (2 mol %).¹⁴

Interestingly, Pd/CaCO₃, a potentially recyclable catalyst, used previously in similar palladium catalyzed additions¹⁵ resulted very inefficient in our case since the reactions turned out to be very unclean and conversion rates to the desired α -(benzyl)- β -keto esters were very low. A possible explanation to this fact could be laid in a combination between the different nature of the catalytic systems. Pd(OAc)₂ in ethanol could follow a mechanism in which it is reduced¹⁶ to soluble Pd(0),¹⁷ which in turn would promote oxidative addition to the substrate. Pd/CaCO₃ would serve as a catalyst reservoir. In the latter case it is now very well documented that the true catalyst is a Pd(II) soluble species formed upon oxidative addition of the substrate.¹⁸ So, a better compromise between catalyst and solvent system must be found to go further in that kind of insoluble catalysts.

Typically, the yields of pure compounds are moderate, except for **8d** (Table 1). In all cases, the desired α -(substituted-aryl)- β -keto esters **8a–f** were purified from the reaction mixture by column chromatography and their structures were assigned based on the usual spectro-



R₁ = CH₂CH₃; R₁ = *p*-NO₂C₆H₄;
or R₁ = Hexyl

Scheme 1. Baylis–Hillman adducts as substrate for a Heck reaction with arenediazonium tetrafluoroborate salts.

Table 1. β -Keto esters from BH adducts via Heck reaction with diazonium salts

| Entry | R ₁ | Diazonium salts (Ar) | Product | Yield (%) |
|-------|--|--|-----------|-----------------|
| 1 | Ethyl | <i>m</i> -O ₂ NC ₆ H ₄ | 8a | 65 |
| 2 | <i>p</i> -O ₂ NC ₆ H ₄ | β -Naphthyl | 8b | 50 |
| 3 | <i>n</i> -Hexyl | <i>o</i> -CH ₃ OC ₆ H ₄ | 8c | 55 |
| 4 | <i>p</i> -O ₂ NC ₆ H ₄ | <i>m</i> -O ₂ NC ₆ H ₄ | 8d | 32 ^a |
| 5 | Cyclohexyl | <i>m</i> -O ₂ NC ₆ H ₄ | 8e | 64 |
| 6 | <i>p</i> -OCH ₃ C ₆ H ₄ | <i>o</i> -CH ₃ OC ₆ H ₄ | 8f | 60 |

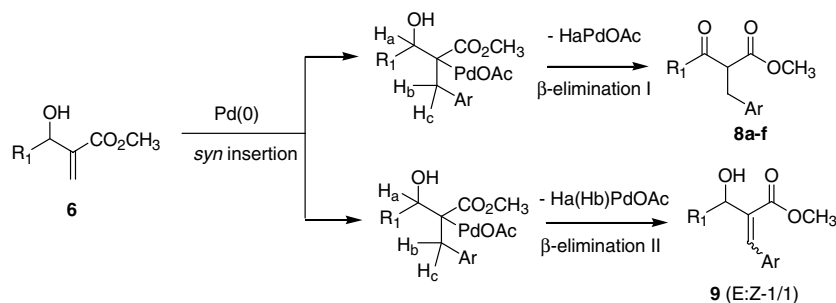
^a Referring to the β -ketoester yield. Total yield was around 60%.

scopic data.¹⁴ As expected, the procedure works quite well for arenediazonium salts with either ED (**8c**) or EW (**8d**) substituents due to the high reactivity of the diazonium nucleofuge. Otherwise, the different nature of the BH adducts employed did not had a marked influence in the formation of the desired β -keto esters.

Interestingly, a small quantity of naphthyl–ethyl ether was detected in the synthesis of compound **8b** (entry 2) as a consequence of the interaction between the naphthyl diazonium salt and the solvent via nucleophilic substitution.

The low yield of **8d** (Table 1, entry 4) was assigned to the concomitant formation of (*E/Z*)-3-(hydroxy-*p*-tolylmethyl)-4-*m*-tolyl-but-3-en-2-one (**9**) as the other major product (30% yield). In this case the Heck reaction between **6a** (R₁ = 4-NO₂-Ph) and diazonium salt (Ar = 3-NO₂-Ph) was found to undergo beta-hydride elimination, affording either compound **8d** or **9** (Scheme 2) in the same proportion (Fig. 1). Maybe the high redox potential of both reactants caused by the presence of nitro groups, drives the reaction pathway in an unspecific manner. As this fact remains unexplained further studies are in progress.

Moreover, the evidence provided by NMR spectroscopy allowed us to confirm that isomers *E* and *Z* for compound **9** are obtained in a 1:1 ratio. This result is consistent with a similar finding reported by Kumareswaran



Scheme 2. β -Elimination and formation of **9**.

et al.⁹ and it could be explained considering that the small difference in energy of both transition states provokes the *syn* elimination of HPdX species, involving both the hydrogens H_b and H_c with almost equal ease.

In summary a simple and expeditious synthesis of α -(substituted-aryl)- β -keto esters has been developed. The use of aerobic conditions, short reaction times and the tolerance towards many structurally diverse reactants offers several advantages over the previously reported methodology.⁹ To our knowledge this is the first example of the application of arenediazonium salts in the preparation of α -(substituted-aryl)- β -keto esters. Further studies to extend the use of diazonium nucleofuges in other palladium catalyzed reactions are currently under research in our group.

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Supplementary data

Supplementary data associated with this article (spectral data for β -keto esters **8b–f** and **9** synthesized in this work) can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.058.

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14. Typical procedure for the synthesis of methyl 2-(3-nitrobenzyl)-3-oxo-pentanoate, **8a**. In a 50 ml reaction flask 3-nitrophenyl diazonium tetrafluoroborate (3 mmol, 0.71 g), Pd(OAc)₂ (0.01 g, 2 mol %) are suspended in 10 ml of ethanol. Subsequently the BH **6a** (R₁ = CH₂CH₃, 3 mmol, 0.42 g) is added and the mixture is heating to 70 °C under stirring. After the reaction is completed the solvent is evaporated and the residue is purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1) to yield 0.52 g, 65% of yellow pale oil. ¹H NMR (DMSO-*d*₆) δ 0.85 (3H, t, *J* = 7.1 Hz, CH₃CH₂-), 2.53 (2H, c, *J* = 7.1 Hz, CH₃CH₂-), 3.10–3.16 (2H, m, -CH₂-Ph), 3.55 (3H, s, -CO₂CH₃), 4.12–4.19 (1H, m, -C(=O)-C(CH₂Ph)-H-C(=O)-), 7.49–8.07 (4H, m, H-Ph) ppm; ¹³C NMR (DMSO-*d*₆) δ 7.3 (CH₃CH₂), 32.7 (CH₃CH₂), 35.0 (CH₂-Ph), 52.2 (-CO₂CH₃), 58.6 (-C(=O)-C(CH₂Ph)-H-C(=O)-), 121.5–147.5 (C-Ph), 169.1 (-CO₂CH₃), 204.9 (CH₃CH₂-C(=O)-). HRMS (ESI, *m/e*) calcd for C₁₃H₁₅NO₅ 265.09502; found 265.09498 [M⁺-Na (23)].
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