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Palladium-catalysed Synthesis of 3-Substituted Coumarins†

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A number of 3-substituted coumarins have been synthesized by palladium-catalysed coupling of 3-bromocoumarin with alkenes, cycloalkenes and alkyne.

The Heck reaction is a palladium-catalysed insertion of vinyl or aryl halides into alkenes, which provides a useful synthetic method for forming carbon–carbon bonds.[1] The catalyst generally used is palladium acetate, although other palladium complexes have been utilised. Tertiary phosphine ligands and an inert atmosphere have been used to prolong the life of the catalyst and the base needed may be a secondary or tertiary amine. The reaction is generally carried out between 50 and 160 °C. In recent years a lot of work has been reported involving the synthetic applications of the Heck insertion reaction as well as the variation of the reaction conditions, the use of arenediazonium salts and triflates, and studies of regio- and stereo-selectivity.[2] The reaction has also been carried out in molten salts,[3] *viz.* tributylhexadecylphosphonium bromide, tetrabutylammonium bromide, *etc.* as well as in aqueous media.[4] Even the use of microwave irradiation in solvent-free conditions has been reported.[5] Asymmetric Heck reactions in the presence of chiral phosphines have been applied in the synthesis of natural products.[6] Palladium-catalysed coupling with alkynes, generally in the presence of copper salts, leads to the formation of enynes and arylacetylenes.[7]

A number of coumarins have diverse biological activities and have been utilised as therapeutic agents in different diseases.[8] Recently the 3-substituted coumarin phenprocoumon and analogous compounds have been identified as active non-peptidic human immunodeficiency virus (HIV) protease inhibitors.[9]

In our continued endeavour[10] in palladium mediated reactions we have exploited the Heck arylation reaction in synthesizing 3-substituted coumarins. Here we report the palladium-catalysed insertion of 3-bromocoumarin[11] into a number of alkenes, cycloalkenes and alkyne to form a variety of 3-substituted coumarins (Table 1). in the case of cycloalkenes (entries 3, 4 and 5) isomerisation of the double bond occurred. Insertion of halobenzene into cyclohexene[12] and 3,4-dihydro-2*H*-pyran[13] to afford the coupled products with isomerisation has been reported. To the best of our knowledge this is the first report of the palladium-catalysed insertion of 3-bromocoumarin into alkenes and alkyne.

Experimental

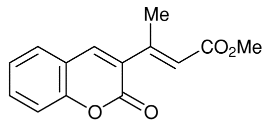
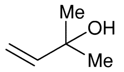
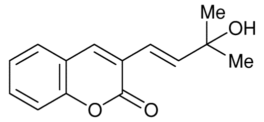
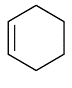
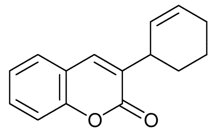
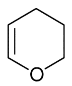
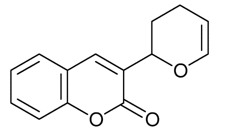
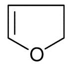
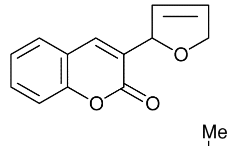
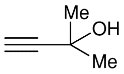
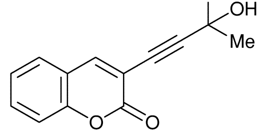
^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a Bruker AM 300L spectrometer operating at 300 and 75 MHz respectively.

General Procedure—(*a*) *With Alkenes.*—A mixture of 3-bromocoumarin (1 mmol), alkene (1.5 mmol), palladium(II) acetate (0.023 mmol), tri-*o*-tolylphosphine (0.028 mmol) and triethylamine (1 ml) was heated at 120 °C for 10 h under an argon atmosphere in a closed vessel. The reaction mixture was cooled, poured into ice-cold water and acidified with dilute HCl. Then it was extracted with dichloromethane, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the product, which was purified by column chromatography on silica gel (60–120 mesh).

(*b*) *With alkyne.*—A mixture of 3-bromocoumarin (1 mmol), alkyne (1.5 mmol), palladium(II) acetate (0.023 mmol), tri-*o*-tolylphosphine (0.028 mmol), copper(I) iodide (0.13 mmol) and triethylamine (1 ml) was heated at 120 °C for 10 h under an argon atmosphere in a closed vessel. The reaction mixture was worked up as described earlier.

Compound **1**: δ_H 7.66 (1 H, s, 4′-H), 7.50–7.18 (4 H, m, Ar-H), 6.36 (1 H, s, 2-H), 3.69 (3 H, s, OCH_3), 2.45 (3 H, s, CH_3). Compound **2**: δ_H 7.63 (1 H, s, 4′-H), 7.47–7.18 (4 H, m, Ar-H), 6.84 and 6.57 (2 H, 2d, *J* 16 Hz, 4-H, 3-H), 1.37 (6 H, s, Me_2); δ_C 160.3, 152.6, 143.0, 137.3, 130.9, 127.5, 124.4, 124.3, 120.0, 119.4, 116.1, 71,0, 29.7. Compound **3**: δ_C 161.2, 152.8, 136.5, 133.8, 130.4, 127.3,

Table 1 Heck reactions of 3-bromocoumarin with alkenes and alkyne

Entry	Alkene or alkyne	Product[a]	Yield (%)[b]
1	MeCH=CHCO2Me		48
2			82
3			91
4			70
5			65
6			66

[a]Found: C, 68.72; H, 4.88. $C_{14}H_{12}O_4$ **1** requires C, 68.85; H, 4.92%. Found: C, 72.98; H, 6.04. $C_{14}H_{14}O_3$ **2** requires C, 73.04; H, 6.09%. Found: C, 79.49; H, 6.14. $C_{15}H_{14}O_2$ **3** requires C, 79.65; H, 6.19%. Found: C, 73.52; H, 5.19. $C_{14}H_{12}O_3$ **4** requires C, 73.68; H, 5.26%. Found: C, 72.74; H, 4.60. $C_{13}H_{10}O_3$ **5** requires C, 72.89; H, 4.67%. Found: C, 73.59; H, 5.18. $C_{14}H_{12}O_3$ **6** requires C, 73.68; H, 5.26%. [b]Isolated yield.

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126.7, 125.7, 124.0, 119.5, 116.1, 34.1, 30.4, 27.2, 25.0. Compound **4**: δ_H (1 H, s, 4′-H), 7.44 (2 H, m, Ar-H), 7.20 (2 H, m, Ar-H), 6.45 (1 H, d, *J* 6.2 Hz, 6-H), 4.86 (1 H, m, 5-H), 4.74 (1 H, m, 2-H), 2.37–1.16 (4 H, m, 3-H, 4-H); δ_C 159.8, 153.0, 143.2, 137.7, 131.0, 129.0, 127.8, 124.3, 119.0, 116.2, 101.3, 71.8, 27.6, 19.6. Compound **5**: δ_H 7.74 (1 H, s, 4′-H), 7.43 (2 H, m, Ar-H), 7.19 (2 H, m, Ar-H), 6.07 and 5.92 (2 H, 2 m, 3-H, 4-H), 5.76 (1 H, m, 2-H), 4.78 (2 H, m, 5-H); δ_C 165.9, 157.8, 137.1, 131.1, 128.1, 127.9, 126.7, 125.4, 124.4, 116.5, 83.1, 75.9. Compound **6**: δ_H 7.79 (1 H, s, 4′-H), 7.49–7.19 (4 H, m, Ar-H), 1.57 (6 H, s, Me_2); δ_C 144.9, 132.1, 127.6, 124.7, 118.8, 116.7, 100.7, 65.5, 31.2.

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