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The Heck reaction under ball-milling conditions

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Abstract

The synthesis of unsaturated unnatural amino acids according to the Heck–Jeffery protocol using a ball-milling procedure is presented. NOE data recorded on the products confirm that the *Z*-isomer is formed. This type of mechano-chemistry provides an efficient, "solvent free" and reliable method for the synthesis of substituted dehydroalanines. These conditions provide patterns of reactivity complementary to conventional procedures.

Keywords: Palladium catalysed Heck-couplings using ball-mill grinding

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1. Introduction

The Heck reaction is one of the most useful palladium-catalysed coupling reactions for the formation of C–C bonds between an aryl halide and an olefin to form styrenic derivatives. This, together with other palladium-catalysed coupling reactions, have been reviewed [1,2]. The wide functional group tolerance of this reaction has allowed rapid syntheses to a large variety of interesting compounds including unsaturated unnatural amino acids using a procedure developed by Jeffery et al. [3]. The methodology for Heck–Jeffery couplings involves extensive reaction times in hot DMF followed by an extractive workup and a chromatographic separation to remove excess olefin [4]. Finally, the remaining DMF is usually removed by co-evaporation with toluene or by lengthy evaporation in vacuo. Hitherto, the Heck–Jeffery conditions involving tetrabutylammonium chloride as phase transfer agent have been the preferred method for coupling of protected amino acrylates, which behaved sluggishly in the standard Heck procedure [10,12]. In order to find a more efficient methodology, we decided to investigate non-solvent ball-mill chemistry. The first investigations in this field were made in the synthesis of diphenols using oxidative coupling [5] and in the synthesis of biaryls using Suzuki conditions [6]. Ball-milling chemistry is of interest because of the mild conditions under which it operates and it has already been applied to reactions such as cyclopropanations of fullerenes [7] and the Wittig reaction [8].

2. Results and discussion

Our results are described and shown in Scheme 1 and Table 1. The protected amino acrylates used in this study were selected among those that were the most successfully used in previous work [4].

All aryl halides are commercially available except for 1,3,5-triiodobenzene, which was synthesized according to the literature procedure [9]. Also the amino acrylates were synthesized according to the literature procedure [10]. The yields given in Table 1 are the optimum result based on three separate reactions for each case carried out in a planetary ball mill.

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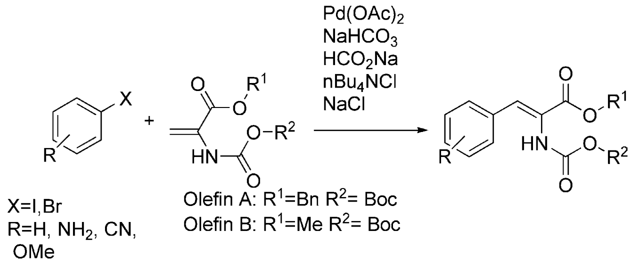

Scheme 1.

Table 1
Optimum yields in the ball-milling Heck–Jeffrey reactions

Arylhalide	Olefin	Yield of product (%)[a]
Iodobenzene	A	76
Iodobenzene	B	77
Bromobenzene	A	57
Bromobenzene	B	57
4-Iodoaniline	B	88
4-Iodoanisole	B	74
3-Iodobenzonitrile	B	28
3-Bromofurane	A	13
2-Iodothiophene	A	25
2-Iodothiophene	B	25
4-Iodonitrobenzene	B	No reaction
2-Bromo-6-methylpyridine	B	No reaction
4-Iodophenol	A	No reaction
Chlorobenzene	A	No reaction
Chlorobenzene	B	No reaction
1,3-Diiodobenzene	A	Complex mixture
1,3,5-Triidobenzene	A	Complex mixture

[a] The reactions were performed and the products were isolated according to the general procedure.

In our ball-milling experiments we adopted the composition of the reaction mixture essentially as given by Calo et al. [11] in their paper on Heck couplings in molten tetra butyl ammonium bromide using conventional laboratory glassware without grinding. Tetra butyl ammonium halides are solids at room temperature but in the molten state they act as ionic liquids that the authors claim to have a stabilizing effect on the catalytic species i.e. Pd(0). Thus, the following ingredients constituted the standard reaction mixture: aryl halide, protected aminoacrylate, $Pd(OAc)_2$, NaCl, $NaHCO_3$, HCO_2Na, and $n Bu_4NCl$. Our preliminary studies confirmed the importance of the tetra butyl ammonium halide, which in our case was $n Bu_4NCl$, for the success of the reaction. Failure to add this ingredient resulted in no reaction whatsoever. Furthermore, the addition of sodium formate as a reductant for Pd(II) improved the yields. In previous ball-milling experiments NaCl was used as an additive presumably as a grinding aid [5,6]. In our experiments we found that the reaction performed best when no NaCl or a relatively small amount of NaCl was added; 5 mg/mg aryl halide seemed to be a good proportion.

Apparently, the ball-milling created conditions that are difficult to obtain under usual conditions. The rotation of the steel balls, certainly create a high pressure in contact with the walls of the container. Thus, high pressure conditions would be possible to test using an ordinary hydraulic press used for making IR-tablets. The reaction between iodobenzene and methyl-2-[(tertbutoxycarbonyl)-amino] acrylate was chosen as a model reaction. Indeed, at 200 kg/cm^2 pressure for 60 min using a preheated anvil (80 °C), the expected coupling product was formed but only in 13% yield. The pressure in the rotating ball-mill is difficult to estimate and it is possible that higher pressure than 200 kg/cm^2 is necessary to reach higher yields.

We also tested if the reaction mixture would give the products on heating to 80 °C for 60 min with and without stirring in ordinary test tubes. This resulted in yields of 33% and 18%, respectively. The reaction temperature was chosen to fit that generated by the ball mill when run at full speed for an hour.

Further, the effect of catalyst loading was probed and it was found that only a 5% yield of coupling product was obtained in the absence of the catalyst ($Pd(OAc)_2$) but already at a catalyst loading of 2 mol% the yield reached 73%. The yield was much the same for catalyst concentrations up to 10 mol%. For practical reasons, the reaction was subsequently run with a catalyst concentration of 5 mol%. The reaction conditions allowed a scale between 0.5 and 5 mmol without loss of yield and quality of the product, e.g. at 5 mmol scale the yield was 78%.

At the initial phase of this project, a few experiments were also performed in a preparative microwave oven but the yields thus obtained were, on average, lower than those of the corresponding ball-milling experiments. Finally, multi-coupling reactions with 1,3-diiodobenzene and 1,3,5-triiodobenzene were attempted but these aryl halides failed to give any significant amount of target product and invariably resulted in a complex mixture of products.

From the model studies, it is apparent that it is not sufficient to simply heat the reaction mixture in a stirred or unstirred vessel or to apply static 200 kg/cm^2 pressure to it. It is most probably the combination of pressure, heat, grinding and stirring that provides the conditions necessary for the successful outcome of the reaction. Furthermore, the same pattern of reactivity as observed in the study of the Suzuki coupling is repeated in the Heck coupling [6]. Thus, coupling of electron-deficient aryl or heteroaryl halides, such as 4-iodonitrobenzene or 2-bromo-6-methylpyridine, which were previously successfully coupled in DMF solution, was not successful in the ball-milling but electron-rich substrates like 4-iodoanisole and 4-iodoaniline were efficient coupling partners. Prior protection of the amine functionality was not necessary and to our knowledge there are no examples of coupling between protected amino acrylates and halo aniline derivatives. 4-Iodoanisole has been used together with 2-acetamidoacrylic acid under ordinary Heck conditions [13], but this methodology seems hampered by low reproducibility and a problematic work-up [10,12].

Ball-milling conditions are undoubtedly very different from conventional conditions, therefore we could not assume that the *E*, *Z*-isomeric ratio would automatically be the same as experiments run under conventional conditions. The products were therefore subjected to NOE analysis. In all cases we found no effect on the vinylic proton when running spectra in amide proton saturation mode, but a NOE effect was observed between the amide proton and the aromatic *ortho* protons. This observation is consistent with the product being in the *Z*-form as demonstrated by our group in earlier studies [10].

The planetary ball-mill methodology is cheap, scalable and may be an efficient alternative to its high-technology counterparts.

3. Experimental

General information: all reagents were used as delivered without further purification. Inorganic salts were dried in an oven at 110 °C overnight. Chromatographic workup was performed on a 24 mm column filled with 25 cm of Matrex 60 Å 35–70 mesh silica. The eluents were heptane:ethylacetate 5:1 for reactions using olefin A and heptane:ethylacetate 3:2 when using olefin B. TLC analyses were performed on Merck silica gel 60 coated aluminium plates with heptane:ethyl acetate 1:1 as eluent. Olefins A and B were synthesized according to the literature procedure [10]. The reactions were performed using a Fritsch Planetary Micro Mill model "Pulverisette 7" housing two stainless steel cups containing eight stainless steel balls each and sealed by a stainless steel lid fitted with a Teflon gasket. NMR spectra were recorded on a Bruker ARX 300 instrument, NOE experiments were recorded in d_6-DMSO at 80 °C on a Bruker DRX 500c, 500 MHz instrument. The delay time was 1 ms, the irradiation time 10 s, the acquisition time 3 s, the repetition time 13 s and the transmitter effect 2 Hz. The samples were degassed in an ultrasound bath for 15 min prior to recording. Melting points were measured on a Gallenkamp melting point microscope and are uncorrected, IR spectra were recorded on a Shimadzu FTIR-8300 instrument and mass spectra were recorded on a JEOL SX-102 mass spectrometer.

3.1. General reaction conditions

To the reaction vessel was added: 1.00 eq. of the aryl halide, 1.05 eq. of the aminoacrylate, 2.50 eq. $NaHCO_3$, 0.20 eq. HCO_2Na, 1.20 eq. $n Bu_4NCl$, 0.05 eq. $Pd(OAc)_2$ and NaCl 5 mg/mg arylhalide. Then 8 steel balls were added to the vessel, which was then purged with argon and closed with lid and Teflon gasket. Two similarly loaded vessels were then fastened securely into place and the cover on the ball mill was closed. The ball mill was then kept at full speed and left thus for 60 min. After the vessels had cooled down, (typically two reactions were run at the same time to balance the rotor of the ball mill), they were taken out of the ball mill and carefully opened. The contents were first scraped out into a beaker and the vessel, including the balls, were washed with 200 ml of acetone. The contents of the beaker were poured into a round-bottomed flask together with 600 mg of silica and the solvent was removed in vacuo. The solid residue absorbed onto silica, was placed on a silica column and eluted with heptane:ethylacetate in proportions described above approximately 250 ml. The results are shown in Table 1. Compounds previously known in the literature were checked by running melting points and ^1H NMR and found to be in good accordance with the literature data [10]. The following new compounds were prepared using this description.

3.2. (Z)-3-(4-Amino-phenyl)-2-tert-butoxycarbonylamino-acrylic acid methyl ester

According to the procedure above: amorphous brown solid; m.p. 148.3–150.1 °C,^1H NMR($CDCl_3$): δ 7.43, 6.64 (AB q, 4H, J_{AB} = 8.4 Hz, Ar–H), 7.27 (s, 1H, HC=), 6.04 (br, 1H, NH), 3.83 (s, 3H, OCH_3), 1.43(s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 166.6, 153.3, 147.9, 132.0, 130.9, 123.9, 121.0, 114.5, 80.6, 60.4, 28.1; HRMS (FAB$^+$) *m*/*e* Calc. for $C_{15}H_{20}N_2O_4$ 292.1423. Found: 292.1419; IR(KBr) cm^{-1}: 3300, 2900, 1699, 1599, 1517. Anal. Calc. for $C_{15}H_{20}N_2O_4$ C, 61.63; H, 6.90; N, 9.58. Found: C, 61.51; H, 7.03; N, 9.49.

3.3. (Z)-2-tert-Butoxycarbonylamino-3-(4-methoxy-phenyl)-acrylic acid methyl ester

According to the procedure above: amorphous white solid; m.p. 107.5–108.7 °C,^1H NMR($CDCl_3$): δ 7.53, 6.88 (AB q, 4H, J_{AB} = 8.7 Hz, Ar–H), 7.51 (s, 1H, HC=), 6.17 (br, 1H, NH), 3.83 (s, 3H, CO_2OCH_3), 3.82 (s, 3H, $ArOCH_3$) 1.42(s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 166.3, 160.3, 153.0, 131.6, 130.5, 126.5, 122.2, 113.9, 80.8, 55.2, 52.4, 28.1; HRMS (FAB$^+$) *m*/*e* Calc. for $C_{16}H_{21}NO_5$ 307.1419. Found: 307.1427; IR(KBr) cm^{-1}: 3209, 2910, 1705, 1637, 1604, 1514. Anal. Calc. for $C_{16}H_{21}NO_5$ C, 62.53; H, 6.89; N, 4.56. Found: C, 62.60; H, 7.04; N, 4.41.

3.4. (Z)-2-tert-Butoxycarbonylamino-3-(3-cyano-phenyl)-acrylic acid methyl ester

According to the procedure above: amorphous white solid; m.p. 102.1–104.0 °C,^1H NMR($CDCl_3$): δ

7.79 (s, 1H, Ar–H), 7.69 (d, 1H, $J_{AB} = 7.5$ Hz, Ar–H), 7.56 (d, 1H, $J = 7.7$ Hz, Ar–H), 7.46 (t, 1H, $J = 7.7$ Hz, Ar–H), 7.21 (s, 1H, HC=), 6.55 (br, 1H, NH), 3.88 (s, 3H, OCH_3), 1.40 (s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 165.4, 151.7, 135.9, 133.6, 132.5, 131.8, 129.1, 125.8, 125.5, 118.4, 112.6, 81.6, 52.9, 28.0; HRMS (FAB^+) *m/e* Calc. for $C_{16}H_{18}N_2O_4$ 302.1266. Found: 302.1272; IR(KBr) cm^{-1}: 3306, 2981, 2229, 1693, 1649, 1493. Anal. Calc. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.39; H, 5.90; N, 9.16.

3.5. (Z)-2-tert-Butoxycarbonylamino-3-thiophen-2-yl-acrylic acid benzyl ester

According to the procedure above: amorphous white solid; m.p. 121.0–122.0 °C,^1H NMR($CDCl_3$): δ 7.77 (br, 1H, HC=), 7.52 (d, 1H, $J = 5.07$ Hz, thienyl), 7.34–7.45 (m, 5H, $J = 6.5$ Hz, Ar–H), 7.34 (d, 1H, $J = 3.25$ Hz, thienyl), 7.09 (t, 1H, H–Ar, $J = 4.96$ Hz), 5.89 (br, 1H, NH), 5.29 (s, 2H, OCH_2Ph), 1.48 (s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 165.1, 153.6, 136.6, 135.7, 133.0, 130.8, 129.0, 128.5, 128.2, 127.0, 121.6, 81.0, 67.1, 28.2; HRMS (FAB^+) *m/e* Calc. for $C_{19}H_{21}NO_4S$ 359.1191. Found: 359.1203; IR(KBr) cm $^{-1}$: 3324, 2968, 2374, 1713, 1622, 1480. Anal. Calc. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.42; H, 6.20; N, 3.57.

3.6. (Z)-2-tert-Butoxycarbonylamino-3-thiophen-2-yl-acrylic acid methyl ester

According to the procedure above: yellow paste,^1H NMR($CDCl_3$): δ 7.71 (br, 1H, HC=), 7.50 (d, 1H, $J = 4.97$ Hz, thienyl), 7.32 (d, 1H, $J = 3.52$ Hz, thienyl), 7.08 (t, 1H, $J = 3.87$, thienyl), 5.86 (br, 1H, N–H), 3.84 (s, 3H, OCH_3), 1.48 (s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 165.7, 153.5, 136.6, 132.8, 130.6, 129.0, 127.0, 121.6, 81.0, 52.4, 28.2; HRMS (FAB + Na) *m/e* Calc. for $C_{13}H_{17}NO_4SNa$ 306.0776. Found: 306.0768; IR(KBr) cm^{-1}: 3230, 2977, 1701, 1627, 1458, 1365, 1265. Anal. Calc. for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.09; H, 5.94; N, 4.94.

3.7. (Z)-2-tert-Butoxycarbonylamino-3-furan-2-yl-acrylic acid benzyl ester

According to the procedure above: white semi solid, ^1H NMR($CDCl_3$): δ 7.72 (s, 1H, furanyl), 7.35–7.43 (m, 5H, $J = 6.3$ Hz, 1H, thienyl), 6.67 (s, 1H, HC=), 6.17 (br, 1H, N–H), 5.27 (s, 2H, O–CH_2Ph), 1.46 (s, 9H, $C(CH_3)_3$; ^{13}C NMR($CDCl_3$): δ 165.2, 153.3, 145.2, 143.6, 135.6, 128.5, 128.3, 128.0, 124.4, 123.3, 120.4, 109.9, 80.8, 67.1, 28.1; HRMS (FAB + Na) *m/e* Calc. for $C_{19}H_{21}NO_5Na$ 366.1317. Found: 366.1344; IR(NaCl) film cm^{-1}: 3332, 2977, 2252, 1699, 1504, 1261. Anal. Calc. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.50; H, 6.18; N, 4.01.

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