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Tetrahedron
Tetrahedron 61 (2005) 4569–4576

Efficient and fast Heck vinylation of 2-bromo-6-methyl pyridines with methylacrylate. Application to the synthesis of 6-methyl cyclopenta[*b*]pyridinone

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Received 10 December 2004; revised 22 February 2005; accepted 3 March 2005

Available online 19 March 2005

Abstract—Heck vinylation of 2-bromo-6-methyl-3-substituted pyridines using η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ complex/toluene and dimethylacetamide (DMA) as co-solvent with methyl acrylate is reported. Electronic and steric effects were investigated engaging diversely 2-bromo-3,6-disubstituted pyridines. As application, a new synthesis of the 6-methyl cyclopenta[*b*]pyridinone building-block connecting Heck vinylation, alkene reduction and Dieckmann condensation is described.

1. Introduction

The Heck palladium-catalyzed vinylation reaction is one of the most attractive tools for the C–C bond formation in organic synthesis.[1] In contrast to Kumada, Suzuki, Stille and others cross-coupling reactions using vinylmetal compounds, the Heck-type olefination is a more functional group tolerant and low cost reaction. Among numerous examples of Heck reactions of halopyridines we counted only, to the best of our knowledge, 11 Heck vinylation reactions of 2-halopyridines with acrylate derivatives allowing good to moderate yields.[2] Nitrogen-based heteroaryls such as pyridines represent highly efficient ligands in-themselves.[3] Thus 2-halopyridines revealed as bad substrates for Heck vinylation probably due to the formation after oxidation step of a pyridyl-bridge palladium dimer preventing further coupling reaction steps.[4,5] Recently we focused our research program on an efficient preparation of numerous 3-substituted-6-methyl-pyridine acrylates **I** applied to a straightforward route to new annulated-cycloalkylpyridines **II**. This framework is present in numerous biologically active compounds[6,2i] such as novel 8-azasteroïd analogues[6a,e] **III** and natural product such as cananodine[7] **IV** (Fig. 1).

Herein, we report a new quantitative and fast kinetic Heck vinylation of a panel of 3-substituted-2-bromo-6-methyl-pyridines using η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ complex/toluene and dimethylacetamide (DMA) as co-solvent. As direct application the 6-methyl cyclopenta[*b*]pyridinone **1** as precursor of novel 8-azasteroïd analogues[6e] was ready prepared via a reduction/Dieckmann condensation sequence.

2. Results and discussion

2.1. Synthesis of 2-bromo-6-methylpyridines

Treatment of 2-hydroxy-6-methylnicotinic acid **2** with $POBr_3$ in refluxed chlorobenzene followed by cold methanol treatment directly provided 2-bromo-6-methyl-nicotinate **3** (Scheme 1). DIBAL reduction of 2-bromo-6-methyl 3-cyanopyridine **4** afforded 2-bromo-3-formyl-6-methyl pyridine **5**. The protected 2-bromo-3-hydroxy-6-methylpyridines **8**, **9** were synthesized in a two steps procedure, bromination of 6-methyl-3-hydroxypyridine **6** affording 2-bromo-3-hydroxy-6-methylpyridine **7** followed by methoxymethyl (MOM) or triflate (OTf) protection of the hydroxyl group (Scheme 1).

2.2. Heck vinylation reaction of 2-bromopyridines with methyl acrylate

We were first interested on the Heck coupling reaction of

Keywords: Heck; Vinylation; Pyridine; Picoline; Cyclopenta[*b*]pyridinone.
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0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.03.008

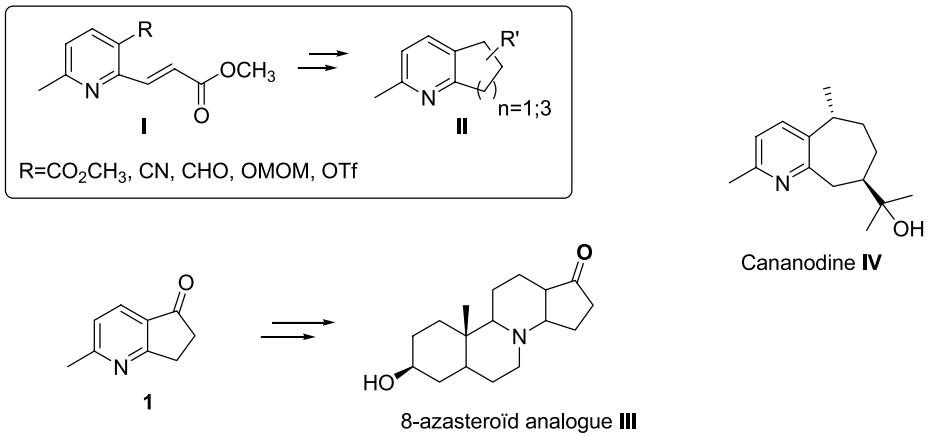
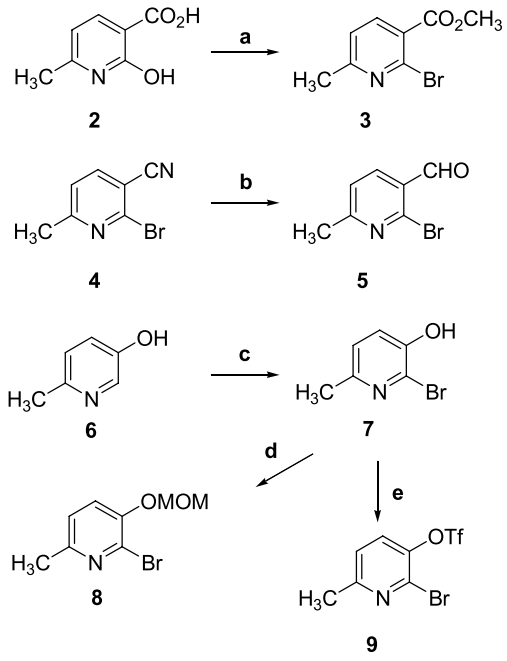


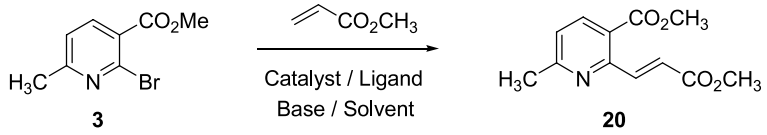
Figure 1.



Scheme 1. (a) $POBr_3$, chlorobenzene, Py then MeOH, O °C, 70% (b) DIBAL-H, toluene, −78 °C, 93% (c) Br_2, Py, 69% (d) MOMCl, DIPEA, CH_2Cl_2, 76% (e) Tf_2O, Py, CH_2Cl_2, 95%.

2-bromo-6-methylnicotinate **3** with methyl acrylate in order to prepare the cyclopenta[c]pyridinone **1**. The initial different assays were summarized in Table 1. Standard Heck conditions for heteroaromatic system [$Pd(OAc)_2$/P(o-tol)$_3$ (1:2), DMF, 130 °C, 24 h][8] were completely inefficient with our substrates (entry 1). Following the Jeffery's conditions[9a,b] using tetrabutylammonium salts[9c] as phase-transfer catalyst and a more polar solvent such as dimethylacetamide (DMA), the 2-pyridyl acrylate compound **20** was obtained only in poor 10% yield (entry 2). Note that any improvement was observed by replacing NaOAc by K_2CO_3 and Cs_2CO_3 bases or over a 48 h refluxing period. We thus decided to use the recent Little and Fu conditions [$Pd_2(dba)_3$/P(^{t}Bu)$_3$ (1:4), Dioxane, reflux, 24 h][10] affording a modest 56% yield of 2-pyridyl acrylate **20** (entry 3). A survey of the literature revealed that Reider and co-workers[2f] carried out the Heck coupling reaction of 6-butyl-2-bromo-3-formyl pyridine with *ter*-butyl acrylate in 85% yield using allylpalladium chloride dimer catalyst, tri-*o*-tolylphosphine and sodium acetate in toluene during a 20 h refluxing period. Using the same conditions the 2-pyridyl acrylate **20** was obtained in 45% yield (entry 4). It should be easily improved using a more polar co-solvent, dimethylacetamide (DMA). Surprisingly complete conversion was obtained in only 5 h (GC-MS monitoring) leading to 84% of pure product (entry 5). Longer refluxing period decreases the yield and higher temperature reaction led to rapid decomposition of the catalyst as black palladium mirror.

Table 1. Heck vinylation of 2-bromo-6-methyl nicotinate with methyl acrylate

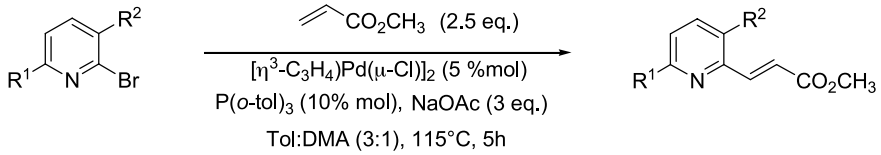


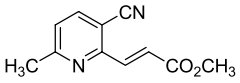
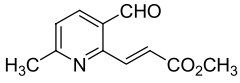
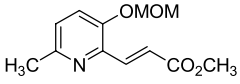
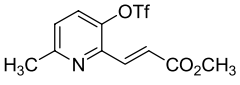
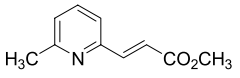
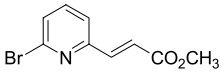
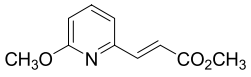
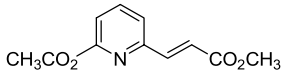
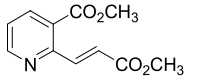
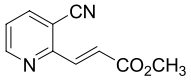
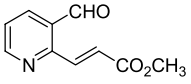
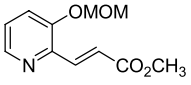
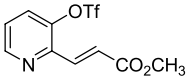
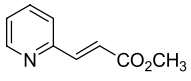
Entry	Catalyst/ligand	Base	Solvent/temperature (°C)	Time (h)	Yield[a]
1	$Pd(OAc)_2$, P(o-tol)$_3$ (1:2)	Et_3N	DMF, 130	24	—
2	$Pd(OAc)_2$, P(o-tol)$_3$ (1:2) Bu_4NHSO_4 (1eq.)	NaOAc	DMA, 100	48	10
3	$Pd_2(dba)_3$, P(^{t}Bu)$_3$ (1:4)	Cs_2CO_3	Dioxane, 85	24	56
4	[(η^3-(C_3H_4)Pd(μ-Cl)]$_2$, (*o*-Tol)$_3$P (1:2)	NaOAc	Toluene, 100	20	45
5	[(η^3-(C_3H_4)Pd(μ-Cl)]$_2$, (*o*-Tol)$_3$P (1:2)	NaOAc	Toluene/DMA (3:1), 100	5	84

[a] Isolated yields, average two runs. DMF: dimethylformamide; DMA: *N*,*N*-dimethylacetamide.

The efficiency of this new Heck vinylation procedure was then tested with a large panel of 3-substituted 2-bromo-6-methyl pyridines substrates (Table 2, entries 1–4). Heck vinylations of 3-carboxy 6-methyl pyridine derivatives **4**, **5** gave excellent 81 and 91% yields (entries 1–2). The same reaction carried out without DMA failed. It should be noted that the original Heck condition [$Pd(OAc)_2$/P(*o*-tol)$_3$ (1:4), DMF, 130 °C, 24 h][8] failed with 3-cyano compound **4** and gave only 8% of 2-pyridyl acrylate **22** starting with the 3-formyl-6-methyl pyridine **5**. In a similar way Little and Fu's conditions [$Pd_2(dba)_3$/P(^{t}Bu)$_3$ (1:4), $CsCO_3$ (1.1 equiv), Dioxane, reflux, 24 h][10] was surprisingly inefficient with the 3-carboxy-6-methyl pyridine substrates **4**, **5**. Protected 3-hydroxy-6-methyl pyridine derivatives **8**–**9** could be easily coupled with methyl acrylate using the new procedure (entries 3,4). Moreover, Heck coupling reaction

Table 2. Heck vinylation of 2-bromopyridine derivatives with methylacrylate



Entry	R^1	R^2		Product		Yield[a]
1	CH_3	CN	**4**		**21**	81
2	CH_3	CHO	**5**		**22**	91
3	CH_3	OMOM	**8**		**23**	82
4	CH_3	OTf	**9**		**24**	61
5	CH_3	H	**10**		**25**	65
6	Br	H	**11**		**26**	92
7	OCH_3	H	**12**		**27**	98
8	CO_2CH_3	H	**13**		**28**	99
10	H	CO_2CH_3	**14**		**29**	36
11	H	CN	**15**		**30**	35
12	H	CHO	**16**		**31**	42
13	H	OMOM	**17**		**32**	27
14	H	OTf	**18**		**33**	9
15	H	H	**19**		**34**	None

[a] Isolated yields, average of two runs.

of the 3-pyridyl triflate **9** with methyl acrylate occurred selectively at the C-2 position. We further extended our procedure to 3 or 6-substituted 2-bromopyridines (entries 5–8, 10–14, Table 2) in order to study the influence of steric and electronic effects. We first observed that the Heck vinylation with methyl acrylate of diversely 2-bromopyridines **11**–**13** substituted at the C-6 position as well as with electron donor and withdrawing electron groups successfully gave good to excellent yields of 2-pyridylacrylates **26**–**28** (entries 5–8, Table 2).

Note that Pd-olefination of 6-methyl-2-bromopyridine **10**, the less hindrered model at C-6 position, occurred in a more modest 65% yield. These results suggest that steric hindrance at C-6 position is the main factor of a successful Heck vinylation probably by preventing the coordination of the nitrogen atom of the pyridine with the catalyst likely avoiding the formation of the unreactive pyridyl-bridge palladium dimer after the oxidation step.[3,4]

Heck vinylation of 2-bromopyridines **14**–**16** only substituted at C-3 position afforded 2-pyridylacrylates **29**–**31** in 36–42% modest yields (entries 10–12). We noticed that a 20 h refluxing period or the use of 20 mol% catalyst do not improve the yield and surprisingly more than 50% of starting material was already recovered. Further assays with protected 3-hydroxy pyridine **17** and 3-pyridyl triflate **18** provided the corresponding 2-pyridyl acrylates **32**, **33** with poor 27 and 9% yields, respectively (entries 13,14). Furthermore, the Heck vinylation of the naked 2-bromopyridine **19** failed under new conditions (entries 15). The results clearly show that the yield of Heck vinylation depend on the chelating power of the group at C-3 position ($CHO > CO_2CH_3 \sim CN > OMOM \sim OTf$) which competes with the nitrogen atom of the pyridine as potential ligand and should prevent partially the formation of the unreactive dimer.[3,4]

2.3. Application to the synthesis of 6-methyl-cyclopenta[*b*]pyridinone

We applied our new procedure to propose the synthesis of the 6-methyl-cyclopenta[*b*]pyridinone **1** which has been only once reported but in a poor 5.5% global yield over four steps from cyclopenta-1,3-dione.[11] A two-steps sequence was thus envisioned from β-2-pyridyl acrylate **20**. Hydrogenation of the double-bond under soft condition provided the diester compound **35** followed by a Dieckmann condensation-decarboxylation[12] sequence to give the 6-methyl-cyclopenta[*b*]pyridinone **1** in a 81% overall yield (Scheme 2).

3. Conclusion

The use of η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ in the presence of toluene associated to dimethylacetamide (DMA) as a co-solvent provided a convenient catalyst system for fast Heck vinylation 2-bromo-3,6-disubstituted pyridines and 2-bromo-6-disubstituted pyridines. The efficiency of the catalyst system with 2-bromo-3-substituted pyridines is however lower. Application to the synthesis of the potential starting material for the synthesis of 8-azasteroïd analogue[6e] 6-methyl-cyclopenta[*b*]pyridinone **1** was achieved via a reduction/Dieckmann condensation sequence in 57% yield over three steps starting from commercially available 2-hydroxy-3-carboxy-6-methyl pyridine **2**. Moreover, Heck vinylation of the 2-bromo-3-triflyl-6-methyl pyridine **9** with methyl acrylate provides selectively the (3-triflyl-6-methyl 2-pyridyl) acrylate **24** which could be a good candidate for the synthesis of cananodine.[7]

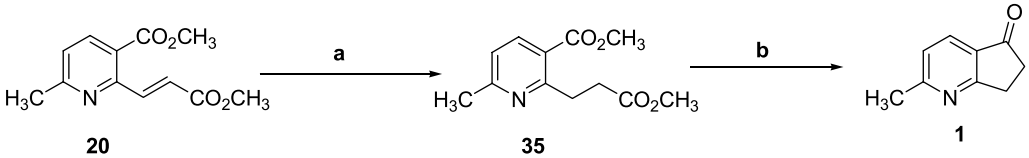
4. Experimental

4.1. General

Tetrahydrofuran (THF), ether (Et_2O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Methanol and ethanol were distilled from magnesium turning. dimethylacetamide was distilled under 4 Å molecular sieves. For flash chromatography, Merck silica gel (70–230 mesh) was used. The melting points were measured on a Kofler melting points apparatus and were not corrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance-300 spectrometer operating at 300 MHz. Commercially available starting materials were used without further purification. Infrared spectra were recorded on a Perkin-Elmer IRTF 1650 spectrophotometer. Elemental analysis of compounds was carried out on a Carlo Erba 1160. Mass spectrum was recorded on a JEOL JMS AX-500 spectrometer, in electronic impact (EI). The starting compounds **4**, **10**–**13**, **15**, **16**, **19** are commercially available. The compounds **14**,[13] **18**[14] are prepared according to the procedures described in literature.

4.2. Synthesis of 2-bromo pyridines substrates

4.2.1. Methyl 2-bromo-6-methylpyridine-3-carboxylate (3). Phosphoryl tribromide (6.14 g, 21.4 mmol) was added by small portion to a solution of nicotonic acid **2** (1.43 g, 9.3 mmol), pyridine (251 μl) and chlorobenzene (30 ml) at



Scheme 2. (a) H_2 (1 atm), Pd/C (10 mol%), MeOH, rt, 94% (b) MeONa (1.5 equiv), THF, refux, 2 h then HCl (4.5 M), reflux 86%.

room temperature under N_2. The mixture was refluxed for 1 h and concentrated under vacuum before treating with an excess of cold methanol (4 ml). The solution was stirred for an additional 1 h and again concentrated under vacuum. The residue was dissolved in (15 ml) and freeze water was added (10 ml). The pH was adjusted to 8 by adding K_2CO_3 before extraction of the product with CH_2Cl_2. The organic layer was washed with 10% aq Na_2CO_3 (10 ml), satd aq. NH_4Cl (10 ml) and dried ($MgSO_4$). After evaporation of the solvent the crude oil was chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to give **3** as a colourless oil (1.50 g, 70%); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 7.02 (d, 1H, $J=7.8$ Hz, H_{5pyr}), 7.80 (d, 1H, $J=7.8$ Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 24.0, 52.4,121.7, 125.8, 139.6, 162.3, 165.0; IR (KBr) ν 2953, 1732 (C=O ester), 1589, 1493, 1345, 1275–1249, 1145, 1051. Anal. Calcd for $C_8H_8BrNO_2$ (230.08): C, 41.77; H, 3.51; N, 6.09. Found: C, 41.73; H, 3.42; N, 6.24%.

4.2.2. 2-bromo-6-methylpyridine-3-carbaldehyde (5). A solution of 2-bromo-6-methylpyridine-3-carbonitrile **4** (1 g, 5.1 mmol) in toluene (15 ml) was cooled at −60 °C. Diisobutylaluminium hydride (3.4 ml of 1.5 M solution in toluene, 5.12 mmol) was added dropwise over a 45 min period while the temperature was maintained under −50 °C. The solution was stirred for 2.5 h at −50 °C and then carefully quenched by the dropwise addition of a mixture of 2 M sulfuric acid (10 ml), toluene (6 ml), and THF (3 ml). The resulted mixture was stirred for 16 h at room temperature and water (15 ml) was added. The organic layer was separated, washed with water (10 ml), brine and concentrated in vacuo to afford **5** as a yellow solid (929 mg, 93%) which was used without further purification; mp 66 °C; ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H, CH_3), 7.27 (d, 1H, $J=7.6$ Hz, H_{5pyr}), 8.07 (d, 1H, $J=7.6$ Hz, H_{4pyr}), 10.30 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 25.1, 123.5, 128.5, 138.4, 145.2, 166.1, 191.4; IR (KBr) ν 3346, 2886, 1979, 1690(C=O ester), 1584, 1341, 1058, *m/z* (EI) 200.0; Anal. Calcd for C_7H_6BrNO (199.98): C, 42.03; H, 3.02; N, 7.00. Found: C, 42.36; H, 2.85; N, 7.21%.

4.2.3. 2-bromo-6-methylpyridin-3-ol (7). A solution of bromide (1.14 ml, 22.2 mmol) in pyridine (20 ml) was slowly added over a 10 min period to a solution of 6-methylpyridin-3-ol **6** (2.2 g, 20.2 mmol) in pyridine (40 ml) at room temperature. The reaction mixture was stirred for an additional 1.5 h and concentrated under vacuum. Water was added (15 ml) until complete precipitation. The beige solid obtained corresponding to **7** was filtered, washed by cool water and dry under reduced pressure (2.6 g, 69%); mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 6.98 (d, 1H, $J=8.0$ Hz, H_{5pyr}), 7.12 (d, 1H, $J=8.0$ Hz, H_{4pyr}), 10.25 (1H, OH); ^{13}C NMR ($CDCl_3$) δ 22.6, 123.6, 124.1, 129.3, 148.8, 149.0; IR (KBr) ν 2923–2431, 1560, 1494, 1293, 1218, 1083; *m/z* (EI) 187.0(98%), 189(100%); Anal. Calcd for C_6H_6BrNO (188.02): C, 38.33; H, 3.22; N, 7.45. Found: C, 38.15; H, 3.14; N, 7.53%.

4.2.4. 2-bromo-3-(methoxymethoxy)-6-methylpyridine (8). Diisopropylethylenediamine DIPEA (2 ml, 11.1 mmol) and chloro(methoxy)methane (565 µl, 7.5 mmol) was added to a solution of 2-bromo-6-methylpyridin-3-ol **7** (700 mg, 3.7 mmol) in dry CH_2Cl_2 (45 ml) at 0 °C under N_2. The solution was stirred for 1 h at 0 °C and for 12 h at room temperature and then quenched with water (10 ml). Extraction with CH_2Cl_2 (2×15 ml), washing with brine, drying with $MgSO_4$ and concentration in vacuo afford **8** a colorless oil (660 mg, 76%) which was used without further purification; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.40 (s, 3H, CH_2OCH_3), 5.12 (s, 2H, OCH_2O), 6.92 (d, 1H, $J=8.3$ Hz, H_5), 7.22 (d, 1H, $J=8.3$ Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 23.4, 56.7, 95.5, 123.2, 124.2, 132.5, 148.8, 152.3; IR (KBr) ν 2958–2926, 1557, 1455, 1269, 1156, 1062, 972; *m/z* (EI) 231.0(98%), 233.0(100%); Anal. Calcd for $C_8H_{10}BrNO_2$ (232.11): C, 41.40; H, 4.34; N, 6.04. Found: C, 41.48; H, 4.21; N, 6.37%.

4.2.5. 2-bromo-6-methylpyridin-3-yl trifluoromethanesulfonate (9). A solution of 2-bromo-6-methylpyridin-3-ol **7** (1 g, 5.3 mmol) and pyridine (800 µl, 10.6 mmol) in CH_2Cl_2 (30 ml) was cooled to 0 °C before adding slowly triflic anhydride (1.08 ml, 6.4 mmol). The mixture was stirred for 1 h at 0 °C and for 12 h at room temperature and quenched by addition of water (10 ml). The pH of the aqueous phase was adjusted to 9 by adding K_2CO_3 before extraction with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$). After evaporation of the solvent, the crude product was chromatographed on silica gel using AcOEt/Petrol (20:80) as eluent to give of **9** as a yellow oil (1.62 g, 95%); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 7.02 (d, 1H, $J=8.3$ Hz, H_5), 7.33 (d, 1H, $J=8.3$ Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 23.9, 1186.7, 123.9, 131.1, 134.7, 142.9, 159.9; IR (KBr) ν 1584–1565, 1431, 1217, 1139, 1052; *m/z* (EI) 319(98%), 321(100%); Anal. Calcd for $C_7H_5BrF_3NO_3S$ (320.09): C, 26.27; H, 1.57; N, 4.38. Found: C, 26.27; H, 1.69; N, 4.49%.

4.2.6. 2-bromo-3-(methoxymethoxy)pyridine (17). The procedure described above, using 2-bromopyridin-3-ol (647 mg, 3.72 mmol) instead of 2-bromo-6-methylpyridin-3-ol, gave **17** (527 mg, 65%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H, CH_2OCH_3), 5.22 (s, 2H, OCH_2O), 7.15 (dd, 1H, $J=8.1$, 4.5 Hz, H_5), 7.36 (dd, 1H, $J=1.1$, 8.1 Hz, H_4), 7.97 (dd, 1H, $J=4.5$, 1.1 Hz, H_3); ^{13}C NMR ($CDCl_3$) δ 56.9, 95.3, 123.5, 123.8, 133.7, 142.9, 151.1; IR (KBr) ν 2959–2933, 1560, 1452, 1414, 1270, 1156, 1092–1053, 971; *m/z* (EI) 217(98%), 219(100%); Anal. Calcd for $C_7H_8BrNO_2$ (218.07): C, 38.56; H, 3.70; N, 6.42. Found: C, 38.59; H, 3.98; N, 6.88%.

4.3. Synthesis of pyridine acrylates (20–34)

4.3.1. Methyl 2-((*E*)-2-(methoxycarbonyl)vinyl)-6-methylpyridine-3-carboxylate (20). A degassed mixture of methyl 2-bromo-6-methylpyridine-3-carboxylate **3** (0.30 g, 1.3 mmol), methyl acrylate (293 µl, 3.3 mmol), allylpalladium chloride dimer $Pd_2(allyl_2Cl_2)$ (24 mg, 0.065 mmol), P(*o*-Tol)$_3$ (40 mg, 0.13 mmol), Na_2CO_3 (320 mg, 3.9 mmol), toluene (2.53 ml) and dimethyacetamide DMA (0.84 ml) was heated in a sealed tube at 115 °C for 5 h. The reaction mixture was filtrated though Celite, washed with AcOEt and concentrated in vacuo. The residue was chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to afford **20** (256 mg, 84%) as a white solid; mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, CH_3), 3.82(s, 3H, CO_2CH_{3pyr}), 3.94 (s, 3H, CO_2CH_{3acry}), 7.09 (d,

1H, $J=15.4$ Hz, H), 7.19 (d, 1H, $J=8.1$ Hz, H_5), 8.11 (d, 1H, $J=8.1$ Hz, H_4), 8.51 (D, 1H, $J=15.4$ Hz, H), ^{13}C NMR ($CDCl_3$) δ 25.2, 52.2, 53.0, 123.6, 123.8, 125.1, 139.2, 141.28, 152.2, 162.3, 166.7, 167.6; IR (KBr) ν 2933–2953, 1714 (C=O ester); 1588, 1466–1438, 1319–1170, 1077 (C–O); *m/z* (EI) 235.0; Anal. Calcd for $C_{12}H_{13}NO_4$ (235.09): C, 61.28; H, 5.56; N, 5.95. Found: C, 61.34; H, 5.39; N, 6.08%.

4.3.2. (*E*)-Methyl 3-(3-cyano-6-methylpyridin-2-yl)acrylate (21). The procedure described above, using 2-bromo-6-methylpyridine-3-carbonitrile **4**, gave **21** (213 mg, 81%) as a yellow solid; mp 138 °C; ^1H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3), 3.86 (s, 3H, CO_2CH_3), 7.25 (d, 1H, $J=8.1$ Hz, H_5), 7.26 (d, 1H, $J=15.2$ Hz, H_{acry}), 7.85 (d, 1H, $J=8.1$ Hz, H_4), 7.97 (d, 1H, $J=15.2$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 25.1, 52.1, 106.8, 116.1, 123.6, 126.4, 137.9, 140.3, 154.1, 163.1, 166.4; IR (KBr) ν 3071–2963, 2225 (C≡N), 1721 (C=O ester), 1583, 1457, 1179; *m/z* (EI) 202.0; Anal. Calcd for $C_{11}H_{10}N_2O_2$ (202.19): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.24; H, 4.34; N, 13.22%.

4.3.3. (*E*)-Methyl 3-(3-formyl-6-methylpyridin-2-yl)-acrylate (22). The procedure described above, using 2-bromo-6-methylpyridine-3-carbaldehyde **5**, gave **22** (243 mg, 91%) as a yellow solid; mp 110 °C; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H, CH_3), 3.85 (s, 3H, CO_2CH_3), 7.20 (d, 1H, $J=15.2$ Hz, H_{acry}), 7.32 (d, 1H, $J=8.0$ Hz, H_5), 8.07 (d, 1H, $J=8.0$ Hz, H_4), 8.47 (d, 1H, $J=15.2$ Hz, H_{acry}), 10.40 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 25.1, 51.9, 124.3, 126.3, 127.0, 137.9, 138.4, 152.7, 163.8, 164.8, 190.0; IR (KBr) ν 2962, 1725, 1699, 1562, 1452, 1300, 1200, 1181; *m/z* (EI) 205.0; Anal. Calcd for $C_{11}H_{11}NO_3$ (205.25): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.22; H, 5.46; N, 6.52%.

4.3.4. (*E*)-Methyl 3-(3-(methoxymethoxy)-6-methylpyridin-2-yl)acrylate (23). The procedure described above, using 2-bromo-3-(methoxymethoxy)-6-methylpyridine **8**, gave **23** (253 mg, 82%): colourless oil; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.44 (s, 3H, CH_2OCH_3), 3.78 (s, 3H, CO_2CH3), 5.19 (s, 2H, OCH2O), 7.00 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.05 (d, 1H, $J=8.7$ Hz, H_5), 7.34 (d, 1H, $J=8.7$ Hz, H_4), 8.05 (d, 1H, $J=15.8$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.0, 52.1, 56.7, 95.0, 121.8, 123.2, 125.4, 138.5, 144.9, 150.7, 151.8, 168.1; IR (KBr) ν 2955–2842, 1717, 1637, 1740–1436, 1320, 1250, 1167; *m/z* (EI) 237.0; Anal. Calcd for $C_{12}H_{15}NO_4$ (237.30): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.64; H, 6.24; N, 5.86%.

4.3.5. 2-((*E*)-2-(Methoxycarbonyl)vinyl)-6-methylpyridin-3-yl trifluoromethanesulfonate (24). The procedure described above, using 2-bromo-6-methylpyridin-3-yl trifluoromethanesulfonate **9**, gave **24** (258 mg, 61%) as a yellow oil; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H, CH_3), 3.82 (s, 3H, CO_2CH_3), 7.15 (d, 1H, $J=15.4$ Hz, H_{acry}), 7.22 (d, 1H, $J=8.6$ Hz, H_5), 7.53 (d, 1H, $J=8.6$ Hz, H_4), 7.83 (d, 1H, $J=15.4$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.5, 52.3, 116.7, 121.0, 125.8, 125.9, 130.3, 134.8, 143.6, 144.6, 159.2, 166.9; IR (KBr) ν 3248, 3079–2850, 1727, 1454–1428, 1216, 1136; *m/z* (EI) 325.0; Anal. Calcd for $C_{11}H_{10}F_3NO_5S$ (325.29): C, 40.62; H, 3.10; N, 4.31; S,9.86. Found: C, 40.63; H, 2.97; N, 4.31; S, 9.74%.

4.3.6. (*E*)-Methyl 3-(6-methylpyridin-2-yl)acrylate (25). The procedure described above, using 2-bromo-6-methylpyridine **10**, gave **25** (150 mg, 65%) as a beige solid; mp 72 °C; ^1H NMR ($CDCl_3$) δ 2.92 (s, 3H, CH_3), 3.75 (s, 3H), 6.87 (d, 1H, $J=15.8$ Hz, H_{acry}); 7.06 (d, 1H, $J=7.5$ Hz, H_5), 7.16 (d, 1H, $J=7.5$ Hz, H_3), 7.52 (d, 1H, $J=7.5$ Hz, H_4), 7.61 (d, 1H, $J=15.8$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.5, 51.7, 121.2, 121.5, 124.0, 136.8, 143.9, 152.1, 158.9, 167.3; IR (KBr) ν 3407, 3026–2960, 1723, 1591–1577, 1473, 1344, 1202; *m/z* (EI) 177.0 Anal. Calcd for $C_{10}H_{11}NO_2$ (177.21): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.78; H, 6.21; N, 7.87%.

4.3.7. (*E*)-Methyl 3-(6-bromopyridin-2-yl)acrylate (26). The procedure described above, using 2,6-dibromopyridine **11**, gave **26** (290 mg, 92%): white powder; mp 138 °C; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H, CO_2CH_3), 6.96 (s, 1H, $J=15.6$ Hz, H_{acry}), 7.33 (d, 1H, $J=7.5$ Hz), 7.42 (d, 1H, $J=7.5$ Hz), 7.55 (d, 1H, $J=7.5$ Hz), 7.56 (d, 1H, $J=15.6$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 52.0, 123.0, 123.4, 128.7, 139.0, 141.6, 142.6, 154.0, 166.9; IR (KBr) ν 2924, 1727, 1646, 1571–1549, 1437, 1320–1300, 1209–1121, 973; *m/z* (EI) 241(100%), 243(98%); Anal. Calcd for $C_9H_8BrNO_2$ (242.11): C, 44.66; H, 3.33; N, 5.79. Found: C, 44.49; H, 3.62; N, 5.72%.

4.3.8. (*E*)-Methyl 3-(6-methoxypyridin-2-yl)acrylate (27). The procedure described above, using 2-bromo-6-methoxypyridine **12**, gave **27** (246 mg, 98%): colourless oil; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H, CO_2CH_3), 3.91 (s, 3H, OMe), 6.89 (d, 1H, $J=8.3$ Hz, H_5), 6.90 (d, 1H, $J=8.3$ Hz, H_3), 6.93 (d, 1H, $J=15.4$ Hz, H_{acry}), 7.51 (d, 1H, $J=8.3$ Hz, H_4), 7.54 (d, 1H, $J=15.4$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 51.7, 53.2, 112.8, 118.4, 121.2, 138.9, 143.2, 150.0, 163.6, 167.4; IR (KBr) ν 3407, 3026–2960, 1723, 1591–1577, 1473, 1344, 1202; *m/z* (EI) 193.0; Anal. Calcd for $C_{10}H_{11}NO_3$ (193.23): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.73; N, 7.07%.

4.3.9. Methyl 6-((*E*)-2-(methoxycarbonyl)vinyl)pyridine-2-carboxylate (28). The procedure described above, using methyl 6-bromopyridine-2-carboxylate **13**, gave **28** (285 mg, 99%): beige powder; mp 112 °C; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, CO_2CH_3), 3.99 (s, 3H, CO_2CH_3), 6.95 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.61 (d, 1H, $J=7.9$ Hz), 7.75 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.85 (d, 1H, $J=7.9$ Hz, H_4), 8.06 (d, 1H, $J=7.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 52.3, 53.4, 123.8, 125.7, 126.7, 138.2, 143.1, 148.7, 153.6, 165.8, 167.1; IR (KBr) ν 2964–2852, 1725, 1458, 1438, 1316–1301, 1245, 1155, 977; *m/z* (EI) 221.0 Anal. Calcd for $C_{11}H_{11}NO_4$ (221.22): C, 59.73; H, 5.01; N, 6.33. Found: C, 59.81; H, 5.14; N, 6.13%.

4.3.10. Methyl 2-((*E*)-2-(methoxycarbonyl)vinyl)pyridine-3-carboxylate (29). The procedure described above, using methyl 2-bromopyridine-3-carboxylate **14**, gave **29** (110 mg, 36%): yellow oil; ^1H NMR ($CDCl_3$) δ 3.81(s, 3H, CO_2CH_3), 3.95 (s, 3H, CO_2CH_3), 7.10 (d, 1H, $J=15.1$ Hz, H_{acry}), 7.34 (dd, 1H, $J=7.9$, 4.9 Hz, H_5), 8.22 (dd, 1H, $J=1.9$, 8.1 Hz, H_4), 8.48 (d, 1H, $J=15.4$ Hz, H_{acry}), 8.73 (dd, 1H, $J=1.9$, 4.9 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.2, 53.1, 123.9, 125.4, 125.9, 138.9, 140.9, 152.7, 152.9, 166.4,

167.5; IR (KBr) ν 3046–2854, 1717 (C=O ester); 1588, 1630, 1560, 1421, 1284–1258, 1083 (C–O); *m/z* (EI) 221.0.

4.3.11. (*E*)-Methyl 3-(3-cyanopyridin-2-yl)acrylate (30). The procedure described above, using 2-bromopyridine-3-carbonitrile **15**, gave **30** (86 mg, 35%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H, CO_2CH_3), 7.23 (d, 1H, J=15.4 Hz, H_{acry}), 7.40 (dd, 1H, J=4.5, 7.9 Hz, H_5), 7.98 (d, 1H, J=15.4 Hz, H_{acry}), 7.97 (dd, 1H, J=1.5, 7.9 Hz, H_4), 8.17 (dd, 1H, J=1.5, 4.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.5, 110.1, 116.0, 122.2, 127.0, 138.1, 140.8, 153.3, 155.1, 166.6; IR (KBr) ν 3077, 2947–2853, 2229, 1724, 1557, 1437, 1312, 1245–1172, 977; *m/z* (EI) 188.0.

4.3.12. (*E*)-Methyl 3-(3-formylpyridin-2-yl)acrylate (31). The procedure described above, using 2-bromopyridine-3-carbaldehyde **16**, gave **31** (104 mg, 42%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, CO_2CH_3), 7.18 (d, 1H, J=15.4 Hz, H_{acry}), 7.46 (dd, 1H, J=7.9, 4.5 Hz, H_5), 8.17 (dd, 1H, J=7.9, 1.5 Hz, H_4), 8.47 (d, 1H, J=15.4 Hz, H_{acry}), 8.80 (dd, 1H, J=4.5, 1.5 Hz, H_6), 10.43 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 52.5, 124.8, 126.9, 129.7, 138.1, 138.8, 153.6, 154.1, 167.2, 190.6, IR (KBr) ν 2957, 1724–1702, 1560, 1438, 1308, 1189,–1170; *m/z* (EI) 191.0; Anal. Calcd for $C_{10}H_9NO_3$ (191.19): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.78; N, 6.64%.

4.3.13. (*E*)-Methyl 3-(3-(methoxymethoxy)pyridin-2-yl)acrylate (32). The procedure described above, using 2-bromo-3-(methoxymethoxy)pyridine **17**, gave **32** (78 mg, 27%): colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_2OCH_3), 3.74 (s, 3H, CO_2CH_3), 5.19 (s, 2H, OCH_2O), 6.95 (d, 1H, J=15.8 Hz, H_{acry}), 7.17 (dd, 1H, J=4.1, 8.6 Hz, H_5), 7.41 (dd, 1H, J=8.6, 1.1 Hz, H_4), 8.05 (d, 1H, J=15.8 Hz, H_{acry}), 8.20 (dd, 1H, J=1.1, 4.1 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.1, 56.8, 94.8, 122.1, 122.5, 125.6, 138.2, 143.1, 143.2, 152.7, 168.0; IR (KBr) ν 3360, 2953–2925, 1714, 1575, 1442, 1309, 1201–1165, 983; *m/z* (EI) 223.0; Anal. Calcd for $C_{11}H_{13}NO_4$ (223.28): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.26; H, 6.43; N, 6.41%.

4.3.14. (*E*)-Methyl 3-(3-(trifluoromethylsulfonyl)pyridin-2-yl)acrylate (33). The procedure described above, using 2-bromopyridin-3-yl trifluoromethanesulfonate **18**, gave **33** (36 mg, 9%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, CO_2CH_3), 7.10 (d, 1H, J=15.4 Hz, H_{acry}), 7.34 (dd, 1H, J=8.3, 4.5 Hz, H_5), 7.65 (d, 1H, J=8.3, 1.5 Hz, H_4), 7.82 (d, 1H, J=15.4 Hz, H_{acry}), 8.57 (dd, 1H, J=1.5, 4.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.5, 114.4, 125.9, 126.2, 130.3, 134.5, 145.3, 145.9, 149.7, 166.8; IR (KBr) ν 2955, 2926, 2854, 1727, 1428, 1308, 1217, 1138, 1075; *m/z* (EI) 311.0.

4.3.15. Methyl 2-(2-(methoxycarbonyl)ethyl)-6-methylpyridine-3-carboxylate (35). A degassed suspension of 10% Pd on charcoal (1.37 g, 1.3 mmol) in a solution of methyl propenoate **20** (3.04 g, 12.92 mmol) in MeOH (120 ml) was vigorously stirred for 3 h at room temperature under H_2. The reaction mixture was filtered though Celite, washed with AcOEt (50 ml) and concentrated in vacuo. The residue was then chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to afford **35** (2.87 g, 94%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H, CH_3), 2.78 (t, 2H, J=7.5 Hz, $CH_2CO_2CH_3$), 3.47 (t, 2H, J=7.5 Hz, $CH_2CH_2CO_2CH_3$), 3.619 (s, 3H, CO_2CH_3), 3.89 (s, 3H, CO_2CH_3), 7.04 (d, 1H, J=7.9 Hz, H_{5pyr}), 8.05 (d, 1H, J=7.9 Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 24.9, 31.9, 33.1, 51.8, 52.5, 121.1, 122.6, 139.3, 160.8, 161.6, 167.1 ($CO_2CH_{3\text{-pyr}}$), 174.2 ($CO_2CH_{3\text{-aliph}}$); IR (KBr) ν 2995–2953, 1727, 1592, 1436, 1369, 1279–1257, 1196–1141, 1081; *m/z* (EI) 237.0; Anal. Calcd for $C_{12}H_{15}NO_4$ (237.21): C, 60.76; H, 6.37; N, 5.90. Found: C, 60.75; H, 6.38; N, 5.86%.

4.3.16. 6,7-Dihydro-2-methylcyclopenta[*b*]pyridin-5-one (1). Sodium methoxide (68 mg, 1.26 mmol) was added to a solution of diester **35** (200 mg, 0.84 mmol) in THF (6 ml) under N_2. The mixture was warmed to reflux during 2 h. The solvent was removed under vacuo and 2 ml of HCl 4.5 M was added. The mixture was stirred 2 h at reflux. The pH was then adjusted to 8 by adding K_2CO_3 before extraction with CH_2Cl_2 The organic layer was washed with 10% aq Na_2CO_3 (5 ml), satd aq. NH_4Cl (5 ml) and dried ($MgSO_4$). After evaporation of the solvent the crude oil was chromatographied on silica gel using AcOEt as eluent to give **3** as a beige oil (107 mg, 86%); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, CH_3), 2.76 (t, 2H, J=6.0 Hz, CH_2CH_2-C=O), 3.22 (t, 2H, J=6.0 Hz, CH_2–C=O), 7.17 (d, 1H, J=7.9 Hz, H_{5pyr}), 7.90 (d, 1H, J=7.9 Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 25.7, 29.1, 36.2, 122.8, 128.4, 132.4, 166.5, 174.9, 205.1 (C=O); IR (KBr) 2925–2854, 1723 (C=O), 1590, 1307, 1107, 1031; *m/z* (EI) 147.0; Anal. Calcd for C_9H_9NO (147.16): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.33; N, 9.23%.

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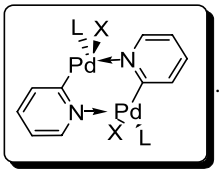

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