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Tetrahedron Letters 44 (2003) 5791–5794

TETRAHEDRON LETTERS

Regio- and selective synthesis of 4,6-disubstituted-2-pyridones

Khalil Cherry,[a] Mohamed Abarbri,[a] Jean-Luc Parrain[b] and Alain Duchêne[a,*]

[a]*Laboratoire de Physicochimie des Interfaces et des Milieux Réactionnels, Faculté des Sciences de Tours, Parc de Grandmont, 37200 Tours, France*

[b]*Laboratoire de Synthèse Organique associé au CNRS (UMR 6009), Faculté des Sciences de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France*

Received 19 May 2003; revised 6 June 2003; accepted 7 June 2003

Abstract—Palladium catalysed regio- and stereoselective annulation of allenyl stannanes by β-iodo vinylic amides gives good yields of the corresponding 2-pyridones. This annulation probably occurs via a Stille reaction/cyclisation sequence.
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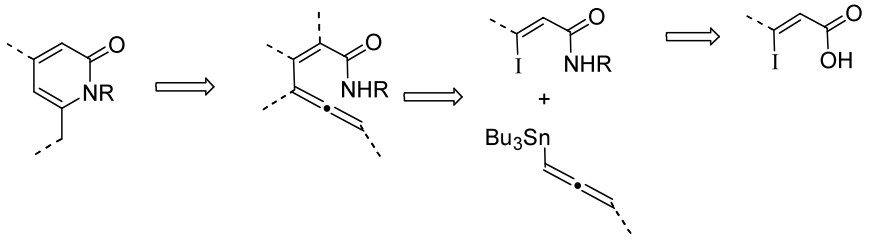
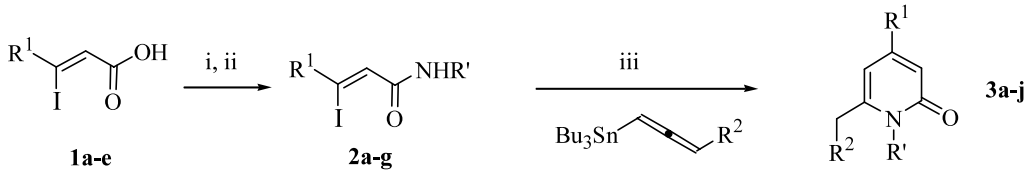
The synthesis of 2-pyridone derivatives is a continuing area of interest due to the number of biologically active molecules containing this moiety.[1] Natural compounds with this structure have emerged during the last ten years as potent antitumor,[2] antifungal,[3] antiviral[4] and psychotherapeutic[5] agents, along with a new antibiotic.[6] Morever, pyridones are key intermediates in the synthesis of the corresponding pyridines.[7] They have been prepared by numerous methods,[8] e.g. oxidation of an *N*-substituted pyridinium salt,[9] and Knovenagel-type reactions,[10] such as cross-condensation of cyanoacetoamide and β-dicarbonyl compounds with basic catalysts or by the reaction of 2-pyrones with amides. Despite this large number of existing methods for their synthesis, new procedures are continuously being developed.[11]

We have previously described the synthesis of dienes or enynes bearing a carboxylic function from β-iodovinylic



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) $(COCl)_2$; (ii) R′NH_2 (70–80%); (iii) $Pd(OAc)_2$ (5% mol), PPh_3 (10% mol), K_2CO_3 (3 equiv.), *n*-Bu_4NBr (2 equiv.), MeCN, 80°C, 3 h.

Keywords: 2-pyridones; tributylstannylallenes; palladium catalyst; coupling reactions.
* Corresponding author. Fax: +33-(0)2-4736-6960; e-mail: duchene@delphi.phys.univ-tours.fr

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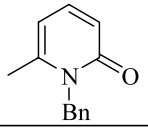
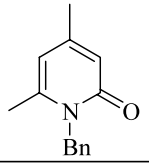
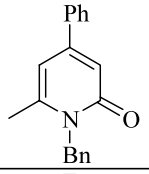
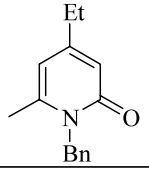
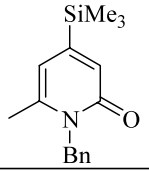
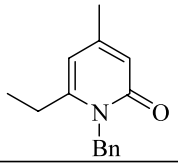
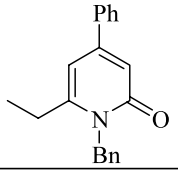
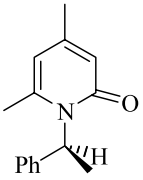
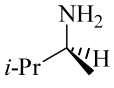
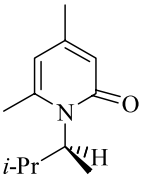
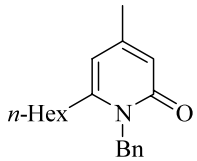
doi:10.1016/S0040-4039(03)01429-1

Table 1. Synthesis of α-pyridones

Entry	R^1	R^2	Amines	Allenylstannane	2-Pyridone	Yield[a] %	N°
1	H	H	Ph-CH_2NH_2	Bu_3Sn		83	**3a**
2	Me	"	"	"		85	**3b**
3	Ph	"	"	"		81	**3c**
4	Et	"	"	"		87	**3d**
5	Me_3Si	"	"	"		79	**3e**
6	Me	Me	"	Bu_3Sn		84	**3f**
7	Ph	"	"	"		85	**3g**
8	Me	"		Bu_3Sn		86	**3h**[b]
9	"	H		"		84	**3i**[c]
10	"	"	Ph-CH_2NH_2	Bu_3Sn *n*-Pent		84	**3j**

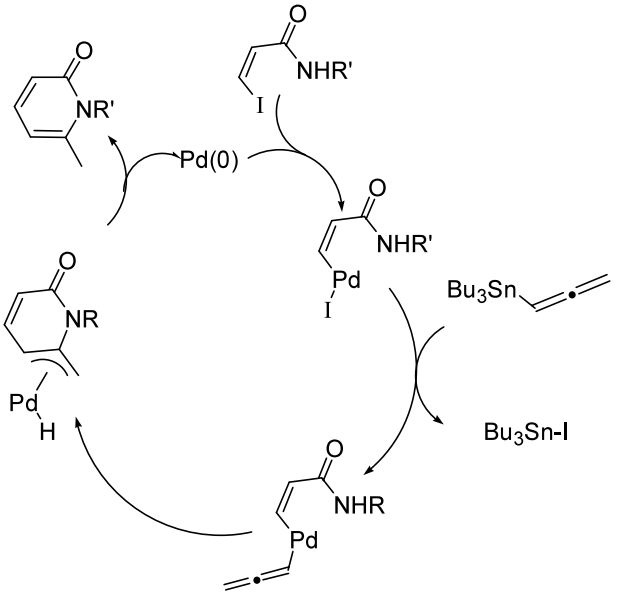
[a] isolated yield; [b] $[\alpha]_D^{23}$ = -210, c = 1% in CH_2Cl_2; [c] $[\alpha]_D^{23}$ = -26, c =1.5 % in CH_2Cl_2

acids and vinyltin or alkynylzinc reagents.[12] We have also reported the stereoselective one-pot synthesis of α-pyrones under palladium complex catalysis by coupling tributylstannylallenes with (*Z*)-iodovinylic acids.[13] Our aim here was to prepare allenylsubstituted alkenoic amides which we believed would exclusively undergo 6-*endo* mode cyclisation mediated by a palladium complex (Scheme 1).

We report here the one-pot synthesis of 4,6-disubstituted-2-pyridones **3a**–**j** by cross-coupling of tributylstannylallenes[14] with (*Z*)-3-substituted-3-iodoprop-2-enamides **2a**–**g** obtained from (*Z*)-iodovinylic acids **1a**–**e** (Scheme 2).[15]

As shown in Table 1, the reaction of tributylstannylallenes with (*Z*)-3-substituted 3-iodopropenoic *N*-protected amides **2a**–**g** under regio- and stereocontrol gave good yields of 4,6-disubstituted-2-pyridones **3a**–**j**. All the experiments were run at 80°C in acetonitrile and in the presence of potassium carbonate and tetrabutylammonium bromide; they were catalysed by the couple: palladium acetate (5% mol)/triphenylphosphine(10% mol), the most efficient catalyst in this case.[16] Using DMF as solvent and other palladium catalysts, low yields of 2-pyridones were obtained. And we obtained optically pure α-pyridones **3h**–**i** from the available optically active amines (entries 8 and 9). In all cases the α-pyridones **3** were obtained without any trace of hexa-2,4,5-trienamide or 2-pyrolone.

A plausible mechanism for the heteroannulation reaction is shown in Scheme 3. First a Stille mechanism would yield 3-allenylprop-2-enamide by oxidative addition, transmetallation and reductive elimination. Cyclisation would then occur via a π-allyl intermediate; the latter would subsequently provide α-pyridone and regenerate the palladium catalyst.[17]



Scheme 3. Proposed mechanism for the formation of 2-pyridones.

In conclusion, under palladium complex catalysis, β-iodo-vinylic-α,β-unsaturated-*N*-protected amides react selectively with tributylstannylallenes via heteroannulation to provide diverse 2-pyridones in excellent yields.

Acknowledgements

We thank the CNRS and MRT for providing financial support, and the 'Service d'analyse chimique du Vivant de Tours' for recording NMR and mass spectra.

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15. *General procedure for the heteroannulation*: Palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (263 mg, 1 mmol), *n*-tetrabutylammonium bromide (6.6 g, 20 mmol) and potassium carbonate (4.14 g, 30 mmol) were successively added to a degassed solution of 3-substituted-3-iodoprop-2-enamide 2 (10 mmol) in anhydrous acetonitrile (40 mL). The mixture was stirred at room temperature for 10 min then allenylstannane (20 mmol) was added. The reaction mixture was stirred and heated at 80°C for 3 h. After conversion was complete (checked by TLC), the reaction was quenched with aqueous NH_4Cl solution, extracted with dichloromethane and dried over magnesium sulfate. After evaporation of the solvents under reduced pressure, the oily mixture was dissolved in the minimum amount of diethyl ether to precipitate *n*-tet precipitate *n*-tetrabutylammonium bromide. After filtration the solution was then treated with ethyl acetate and a 0.5M solution of potassium fluoride at 0°C for 30 min to precipitate the tributyltin iodide formed. The resulting mixture was filtered through a Celite path and, after usual treatments, the crude products were chromatographed on silica gel (petroleum ether/triethylamine 99/1 followed by petroleum ether/diethyl ether/triethylamine 80/19/1) to yield compounds **3a**–**j**. **3a**: oily, IR: 3062, 3029, 2955, 2922, 1675, 1624, 1573; ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.13 (s, 3H), 4.53 (s, 2H), 5.56–5.60 (m, 1H), 6.2 (d, $J=9.7$ Hz, 1H), 6.59 (dd, $J=9.7$, 9.6 Hz, 1H), 7.25–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 19.8, 50.5, 101.4, 118.1, 126.8, 128.4 (2C), 128.7 (2C), 133.2, 141.5, 153.7, 158.6; MS (70 eV) m/z: 199 ($M^{+\bullet}$, 6), 91 (100), 65 (29), 39 (13). **3b**: oily, IR: 3062, 3029, 2953, 2918, 1682, 1628, 1583; ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 1.95 (d, $J=1.1$ Hz, 3H), 2.1 (s, 3 H), 4.52 (s, 2H), 5.46 (q, $J=1.1$ Hz, 1H), 6.0 (s, 1H), 7.23–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 19.6, 21.3, 50.4, 104.8, 114.6, 126.7, 128.4 (2C), 128.7 (2C), 141.7, 144, 154.4, 157.4; MS (70 eV) m/z: 213 ($M^{+\bullet}$, 7), 91 (100), 65 (16), 43 (10), 39 (8). **3c**: Mp = 97–99°C, IR (KBr): 3061, 3029, 2955, 2919, 1673, 1623, 1582, ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.16 (s, 3H), 4.53 (s, 2H), 5.92 (s, 1H), 6.44 (s, 1H), 7.20–7.63 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 20.0, 50.9, 101.7, 113.8, 126.4 (2C), 126.9, 128.5 (2C), 128.8 (2C), 129.3 (2C), 129.7, 137.15, 141.6, 144.6, 154.3, 158.4; MS (70 eV) m/z: 275 ($M^{+\bullet}$, 20), 158 (14), 91 (100), 65 (23), 43 (13). **3d**: oily; IR: 3065, 3025, 2969, 2924, 1682, 1622, 1582; ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 1.13 (t, $J=7.5$ Hz, 3H), 2.11 (s, 3H), 2.25 (q, $J=7.5$ Hz, 2H), 4.53 (s, 2H), 5.48 (s, 1H), 6.02 (s, 1H), 7.24–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 12.5, 19.6, 28.1, 50.5, 103.8, 113.1, 126.7, 128.4 (2C), 128.7 (2C), 141.8, 149.5, 154.6, 157.4; MS (70 eV) m/z: 227 ($M^{+\bullet}$, 24), 121 (24), 91 (100), 65 (27), 39 (10). **3i**: oily, $[\alpha]_D^{23}=-26$ (c 0.01 g/cm^3, CH_2Cl_2); IR: 3070, 2961, 2927, 1683, 1632, 1589; ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 0.82 (d, $J=4.7$ Hz, 3H), 0.86 (d, $J=4.7$ Hz, 3H), 1.00 (d, $J=6.4$ Hz, 3H), 1.48–1.65 (m, 1H), 1.83 (d, $J=1.3$ Hz, 3H), 1.97 (s, 3H), 3.41–3.54 (m, 1H), 5.30 (q, $J=1$ Hz, 1H), 5.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 18.7, 19.5 (2C), 20.1, 21.1, 34.9, 55.8, 104.1, 114.7, 143.2, 152.4, 157; MS (70 eV) m/z: 193 ($M^{+\bullet}$, 3), 150 (52), 96 (34), 71 (24), 53 (14), 43 (100), 41 (23), 39 (15).
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