Synthesis of Substituted Imidazo[1,2-*h*][1,7]naphthyridines as H^+/K^+-ATPase Inhibiting Drug Precursors via Directed *ortho*-Metalation of Imidazo[1,2-*a*]pyridines

Jörg Senn-Bilfinger,* Bernhard Kohl, Georg Rainer, Wilm Buhr, Hans Christof Holst, Peter Jan Zimmermann

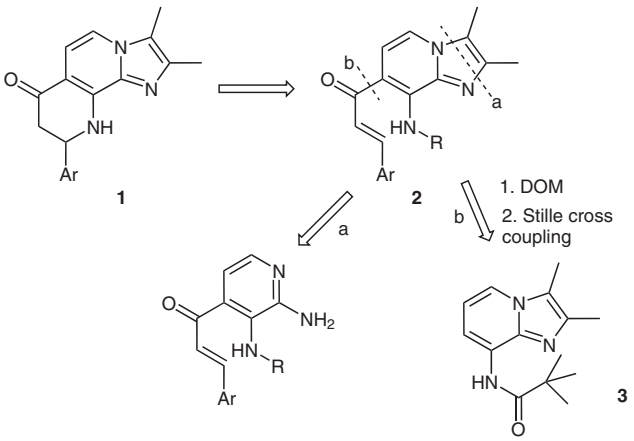
ALTANA Pharma AG, now Nycomed GmbH, Byk-Gulden-Str.2, 78467 Konstanz, Germany
Fax +49(7531)8492505; E-mail: joerg.senn-bilfinger@nycomed.com

Received 28 May 2008

Abstract: Selective directed *ortho*-metalation (DOM) of 2,3-dimethyl-8-(pivaloylamino)imidazo[1,2-*a*]pyridine in the 7-position was achieved with *tert*-butyllithium. Subsequent reaction of the lithiated derivative with tributylchlorostannane to the corresponding 7-trialkylstannyl analogue and palladium-catalyzed Stille acylation with 3-arylpropenoic acid chlorides in the presence of lithium chloride gave the corresponding 7-acylated imidazopyridines in good yields. Cyclization to the target imidazonaphthyridines, which are precursors in the synthesis of gastric H^+/K^+-ATPase inhibiting drugs, was achieved by treatment with strong acid. For scaled-up production of 2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-*h*][1,7]naphthyridin-7(8*H*)-one, a tin-free process has been developed. Accordingly, the 7-lithiated 2,3-dimethyl-8-(pivaloylamino)imidazo[1,2-*a*]pyridine was reacted directly with cinnamaldehyde and the resultant alcohol oxidized with manganese dioxide to give the unsaturated 7-acylated imidazopyridine.

Key words: cyclizations, directed *ortho*-metalation, H^+/K^+-ATPase, lithiation, Stille reaction

Directed *ortho*-metalation (DOM) is one of the most powerful and versatile methods for the rapid synthesis of polyfunctionalized compounds in synthetic organic chemistry.[1] In connection with palladium-catalyzed cross-coupling reactions, this methodology has also vastly enlarged the chemical arsenal of synthetic methods en route to highly functionalized aromatic and heteroaromatic compounds with high diversity in medicinal chemistry.[2] In this account, we report on the use of the DOM reaction and subsequent Stille cross-coupling reaction as key steps in the synthesis of side-chain rigidized 9-arylimidazonaphthyridines **1**.[3] These derivatives were targeted as precursors for the synthesis of H^+/K^+-ATPase inhibiting compounds to be developed as gastric antisecretory drugs. The retrosynthetic analysis depicted in Scheme 1 reveals that the target structure **1** may be derived by cyclization of 7-(prop-2-enoyl)imidazo[1,2-*a*]pyridine **2**, analogously to known procedures for the preparation of quinolones.[4] The general route towards substituted imidazo[1,2-*a*]pyridines comprises the condensation of appropriately substituted 2-aminopyridines with α-halocarbonyl compounds.[5] However, the starting 4-acyl-2,3-diaminopyridines are not easily accessible by conventional methods (Scheme 1, route a). Furthermore, these are prone to a multitude of side reactions due to the lowered nucleophilicity of the pyridine nitrogen. Therefore, we decided to introduce the 7-substituent in **2** via DOM at a later stage in the synthesis, when the imidazo[1,2-*a*]pyridine core had already been elaborated. Since earlier reports on the metalation of aminopyridines demonstrated that the pivaloylamino (2,2-dimethylpropanoylamino) group is a useful *ortho*-directing group,[6] and is also assisting in the cyclization reaction to the imidazo[1,2-*a*]pyridine, we envisioned the readily available 8-(pivaloylamino)imidazo[1,2-*a*]pyridine **3** as a suitable starting point. The introduction of a 7-trialkylstannyl group by DOM reaction of imidazo[1,2-*a*]pyridine **3** would then allow further Stille cross-coupling reactions with substituted cinnamoyl chlorides, giving access to various 7-acyl-substituted imidazo[1,2-*a*]pyridines **2** (Scheme 1, route b).[7,8]

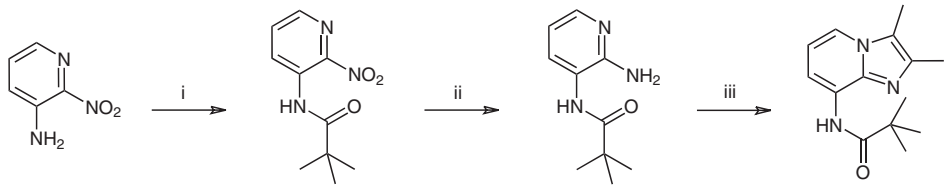


Scheme 1 Retrosynthetic analysis of **1**

Thus, reaction of commercially available 2-nitropyridin-3-amine (**4**) with pivaloyl chloride in the presence of triethylamine provided the 3-(pivaloylamino) derivative **5**, which was hydrogenated to give the protected diaminopyridine **6**. Subsequent condensation with 3-chlorobutan-2-one and basic workup of the precipitated hydrochloride **3**·HCl led to 8-(pivaloylamino)imidazo[1,2-*a*]pyridine **3** in high overall yield (Scheme 2).

Having obtained the 8-(pivaloylamino)imidazo[1,2-*a*]pyridine **3**, the sequence of DOM and subsequent reaction of the lithiated intermediate with tributylchlorostannane was investigated. In a first approach, the imidazo[1,2-*a*]pyridine **3** was reacted with *n*-butyllithium (3 equiv) com-

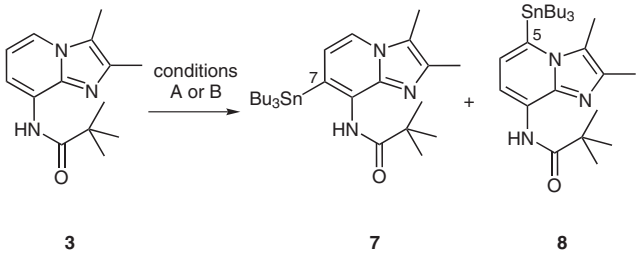
SYNTHESIS 2008, No. 19, pp 3065–3070
Advanced online publication: 05.09.2008
DOI: 10.1055/s-2008-1067264; Art ID: Z12608SS



Scheme 2 *Reagents and conditions*: (i) *t*-BuCOCl, Et_3N, toluene, reflux, 3.5 h; (ii) H_2, 5% Pd/C, MeOH, 40 °C, 5 h; (iii) 1. 3-chlorobutan-2-one, toluene, reflux, 6 h; 2. concd NH_3, H_2O, r.t., 69% from **4**.

plexed by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (3 equiv)[6b] at –78 °C followed by addition of tributylchlorostannane at 0 °C. After one hour at room temperature, a 1:1 mixture of the 5- and 7-tributylstannyl derivatives **7** and **8** was obtained, along with a large amount (50%) of unreacted starting material **3** (Scheme 3, condition A). Further attempts to increase the conversion of **3** by extending the reaction time after the addition of *n*-butyllithium or by running the reaction at higher temperature proved unsuccessful. However, when the metalation of compound **3** was carried out with *tert*-butyllithium (3 equiv) at –78 °C and the intermediate trapped with tributylchlorostannane, the conversion of starting material **3** increased (90%) and the ratio of the regioisomeric stannanes **7** and **8** was clearly improved to 9:1 (Scheme 3, condition B).

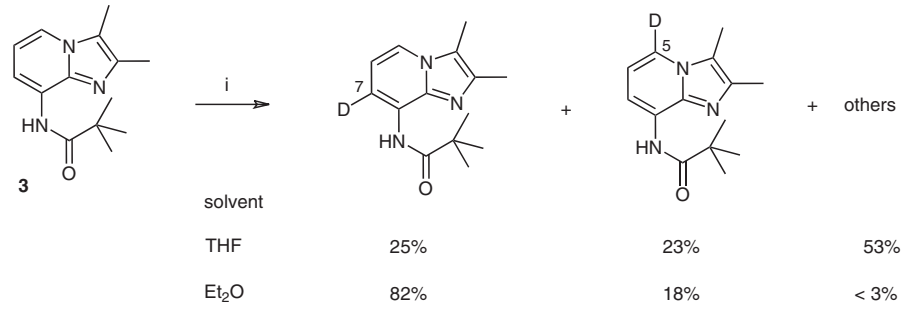
Additional experiments were conducted to investigate the influence of the solvent. Therefore, the imidazo[1,2-*a*]pyridine **3** was reacted with *tert*-butyllithium (2.8 equiv) in



Scheme 3 *Reagents and conditions*: (A) 1.6 M *n*-BuLi in hexane (3 equiv), TMEDA (3 equiv), Et_2O, –78 °C to 0 °C followed by addition of Bu_3SnCl (3 equiv), 30 min, then r.t., 1 h, crude 1:1 mixture of **7** and **8**; (B) 1.5 M *t*-BuLi in pentane (3 equiv), Et_2O, –78 °C followed by addition of Bu_3SnCl (3 equiv), 1h , then r.t., overnight, crude mixture of **7** and **8,** 9:1; **7** was obtained in 41% yield.

tetrahydrofuran at –75 °C and the resulting solution was subsequently quenched with deuterium oxide. The analysis of the crude reaction product by ^1H NMR spectroscopy revealed that the deprotonation had occurred unselectively in the 5- and 7-positions of **3** giving rise to a 1:1 mixture of the 5- and 7-deuterated derivative together with various bis(deuterated) products. On the other hand, when diethyl ether was used instead of tetrahydrofuran, deprotonation again occurred predominantly in the 7-position of **3** to give a 4:1 mixture of the 7- and 5-deuterated derivative, respectively (Scheme 4). Presumably the kinetically preferred 7-deprotonated anion is not exposed to the equilibrium with the thermodynamically favored 5-deprotonated anion, since the former anion precipitates in diethyl ether at the low reaction temperature.

With these excellent results in hand, we began our studies on the Stille cross coupling of the 7-(tributylstannyl)imidazo[1,2-*a*]pyridine **7** with substituted cinnamoyl chlorides **9a–d** (Scheme 5). Although the Stille cross-coupling reaction of aryl- and heteroarylstannanes with acyl chlorides has been extensively studied over the past three decades,[9] only a few examples of such reactions with α,β-unsaturated acyl chlorides are described in the literature.[10] Initial experiments concerning the cross coupling of 7-(tributylstannyl)imidazo[1,2-*a*]pyridine **7** with cinnamoyl chloride **9a** were carried out with dichlorobis(triphenylphosphine)palladium (10%) in tetrahydrofuran at 50–60 °C and led to complete destannylation of the starting material **7**. Several modifications of the reaction conditions, including change of catalysts [$Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, $PdCl_2$(dppf)] or solvent (toluene, NMP), were unsuccessful. However, when bis(acetonitrile)dichloropalladium [$PdCl_2(MeCN)_2$, 15%] was used as a catalyst in the presence of an excess of cinnamoyl



Scheme 4 Lithiation of **3**. *Reagents and conditions*: 1.7 M *t*-BuLi in pentane (2.8 equiv), THF or Et_2O, –75 °C, 15 min followed by quenching with D_2O.

chloride (3 equiv), the hydrochloride of the product **2a** precipitated from the reaction mixture on cooling to yield 26% of **2a**. This result prompted us to examine briefly the influence of chloride being present in the reaction mixture on the conversion of starting material **7**. Since it is also known that added halides can strongly influence reaction rates and that the presence of lithium chloride is often necessary when coupling aryl triflates in ethereal solvents,[11] we added lithium chloride to the reaction mixture in order to improve the conversion of **7**. In fact, running the reaction with $PdCl_2(MeCN)_2$ (10%), cinnamoyl chloride (1.1 equiv), and lithium chloride (1.1 equiv) as additive resulted in almost complete conversion of the starting material **7** (>90%). Under optimized reaction conditions and with tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] as catalyst, the desired product **2a** was isolated in 66% yield on a multigram scale. Likewise, further substituted cinnamoyl chlorides **9b–d** were reacted with stannane **7** under similar conditions as for **2a** to provide the corresponding 7-acylated compounds **2b–d** in moderate yields (Table 1).

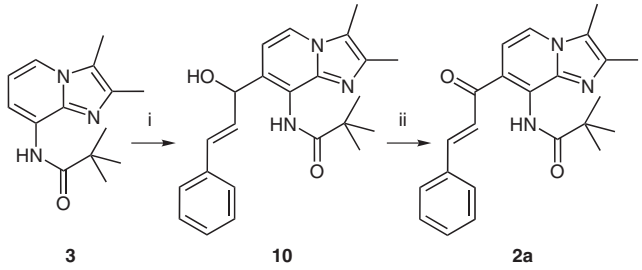
Table 1 Synthesis of Compounds **1a–d** and **2a–d**

Ar	Product	Yield (%)	Mp (°C)	Product	Yield (%)	Mp (°C)
Ph	**2a**	66	177–179	**1a**	69	138–140
2-ClC_6H_4	**2b**	4	158–160	**1b**	73	80–82
2,6-$Cl_2C_6H_3$	**2c**	50[a]	n.d.	**1c**	41	248–249
2-$CF_3CC_6H_4$	**2d**	50[a]	n.d.	**1d**	41	184–185

[a] Crude yield.

The α,β-unsaturated acyl-substituted imidazo[1,2-*a*]pyridines **2a–d** were then finally cyclized to the target compounds **1a–d** under acidic conditions. Thus, heating compounds **2a–d** with concentrated hydrochloric acid (**2a**, **2b**) or 50% sulfuric acid (**2c**, **2d**) led to cleavage of the pivaloylamino protective group and concomitant cyclization to the respective 9-arylimidazonaphthyridines **1a–d** in good to moderate yields (Scheme 5, Table 1).[3]

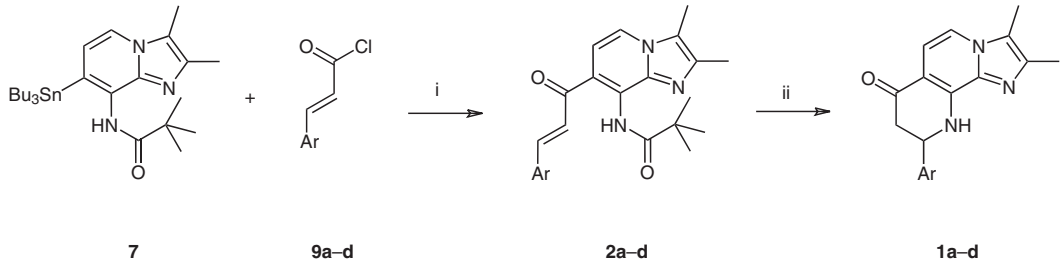
Finally, we focused on the scaleup of compound **1a** which was required in multigram amounts for further modifications to form active H^+/K^+-ATPase inhibitors.[3] For this purpose, it was necessary to establish a tin-free process in order to avoid the handling of environmentally hazardous tin organyls on large scale and contamination of the final product with traces thereof. In fact, reaction of the lithiated derivative of compound **3** with cinnamaldehyde to the alcohol **10** and subsequent oxidation with manganese dioxide proved to be an alternative approach and delivered the 7-cinnamoyl-substituted imidazo[1,2-*a*]pyridine **2a** in good yield (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) 1. 1.5 M *t*-BuLi in pentane, Et_2O, –78 °C; 2. PhCH=CHCHO, –78 °C, 1 h and r.t., 1 h, 60%; (ii) MnO_2, $CHCl_3$, r.t., 16 h, 75%.

The straightforward and convenient synthesis of a series of substituted imidazonaphthyridines serving as precursors of gastric H^+/K^+-ATPase inhibiting drugs has been successfully worked out. Selective directed *ortho*-metalation (DOM) of 2,3-dimethyl-8-(pivaloylamino)imidazo[1,2-*a*]pyridine **3** with *tert*-butyllithium and tributylchlorostannane, followed by Stille cross-coupling and acid-catalyzed cyclization of the corresponding unsaturated 7-acyl compounds led to the highly substituted imidazo[1,2-*h*][1,7]naphthyridines **1a–d**. The development of a scaled-up route for compound **1a** avoiding toxic tin organyls proved to be possible by direct reaction of the lithiated derivative of **3** with cinnamaldehyde followed by clean oxidation of the hydroxy function of alcohol **10**. The synthesis of enantiomerically pure analogues of **1** as well as their conversion into highly active H^+/K^+-ATPase inhibitors, which eventually led to the discovery of the clinically studied analogue Soraprazan,[12] will be described in a forthcoming full paper.

Melting points were taken in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. All NMR spectra were recorded in DMSO-d_6 on a Bruker DPX 200 or Avance 400 spectrometer and are referenced to TMS or the ^{13}C signal of the solvent (δ = 39.5). The ^{13}C peak assignments are based on 2D HSQC and



Scheme 5 *Reagents and conditions*: (i) $Pd_2(dba)_3$ (7–12.5%), ArCH=CHCOCl (1–1.28 equiv), LiCl (1–1.28 equiv), THF, 60 °C; (ii) **2a**, **2b**: concd HCl, 100 °C, 4 h; **2c**, **2d**: 50% H_2SO_4, 100 °C, 3–4 h; for details see experimental part.

HMBC spectra. Elemental analyses were performed on a Carlo Erba 1106 C, H, N analyzer at the Institut für Organische Chemie, Universität Stuttgart.

2,2-Dimethyl-*N*-(2-nitropyridin-3-yl)propanamide (5)

To a suspension of 2-nitropyridin-3-amine (**4**, 12.0 kg, 86.3 mol) in toluene (36 L) were successively added Et_3N (14.7 L, 105 mol) and trimethylacetyl chloride (12.8 L, 105 mol). The mixture was refluxed for 3.5 h and then cooled to 25 °C and extracted with H_2O (14.4 L). The organic layer was separated, washed with H_2O (14.4 L), and evaporated. Co-evaporation with MeOH (6 L) left an oily residue of crude **5** (20.5 kg) which was used directly in the next step.

***N*-(2-Aminopyridin-3-yl)-2,2-dimethylpropanamide (6)**

To a soln of crude **5** (20.5 kg) in MeOH (100 L) was added 5% Pd/C (0.96 kg, 50 wt% in H_2O) and the mixture was hydrogenated (1–1.5 bar H_2) while the inner temperature was maintained at 35–40 °C. After complete uptake of H_2, stirring was continued overnight at r.t. The catalyst was filtered off, washed with MeOH (6 L) and the filtrate was evaporated. After co-evaporation with toluene (36 L), a precipitate began to form, which was collected and washed with toluene to yield **6** (10.97 kg). A second crop of the product **6** (3.7 kg) was obtained from the mother liquor on evaporation. The combined crude product (14.67 kg) was used directly in the next step.

***N*-(2,3-Dimethylimidazo[1,2-*a*]pyridin-8-yl)-2,2-dimethylpropanamide Hydrochloride (3·HCl)**

To a suspension of crude **6** (14.67 kg) in toluene (96 L) was added 3-chlorobutan-2-one (96 wt%, 11.8 L, 112 mol) and the mixture was refluxed using a Dean–Stark trap. After 1 h, additional 3-chlorobutan-2-one (1.4 L, 13 mol) was added and heating was continued for 6 h. After removal of 8–10 L toluene by distillation, precipitation of **3**·HCl began and the mixture was allowed to cool to r.t. overnight. The precipitate was collected, washed with toluene (6 L) and dried in vacuo at 50–60 °C to yield **3**·HCl (16.9 kg, 70% based on **4**).

***N*-(2,3-Dimethylimidazo[1,2-*a*]pyridin-8-yl)-2,2-dimethylpropanamide (3)**

To a suspension of **3**·HCl (260 g, 0.92 mol) in H_2O (1 L) and CH_2Cl_2 (0.4 L) was added concd NH_3 (75 mL) until pH 10. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with H_2O (2 ×), dried (Na_2SO_4), and evaporated to half of its volume. Upon addition of light petroleum ether, the product began to crystallize. The precipitate was collected, washed with light petroleum ether, and dried in vacuo at 45 °C to yield **3** as a beige solid (220 g, 97%); mp 91–93 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 [s, 9 H, $(CH_3)_3$], 2.33 (s, 3 H, 2-CH_3), 2.38 (s, 3 H, 3-CH_3), 6.84 (dd, J_{HH} = 7.5, 6.8 Hz, 1 H, H6), 7.86 (dd, J_{HH} = 7.5, 0.8 Hz, 1 H, H7), 7.89 (dd, J_{HH} = 6.8, 0.8 Hz, 1 H, H5), 8.85 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.90 (3-CH_3), 12.92 (2-CH_3), 27.08 [3 C, C(CH_3)$_3$], 39.43 [$C(CH_3)_3$], 108.60 (C7), 111.40 (C6), 117.18 (C3), 118.49 (C5), 125.85 (C8), 136.95 (C8a), 137.31 (C2), 176.49 (C=O).

Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.42; H, 7.85; N, 17.31.

***N*-[2,3-Dimethyl-7-(tributylstannyl)imidazo[1,2-*a*]pyridin-8-yl]-2,2-dimethylpropanamide (7)**

To a soln of **3** (53.5 g, 0.22 mol) in anhyd Et_2O (1.3 L) was added dropwise 1.5 M *t*-BuLi in pentane (0.44 L, 0.66 mol) at –78 °C over a period of 1.5 h. After a further 1 h at –78 °C, Bu_3SnCl (187 mL, 0.66 mol) was slowly added to the suspension and stirring was continued at –78 °C for 1 h and at r.t. overnight. The mixture was poured into H_2O and extracted with Et_2O (2 ×). The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (light petroleum ether–EtOAc, 3:2) to give **7** (54.9 g, 41%) as an oil with a purity of 87% (^{1}H NMR). The product was used without further purification in the next step.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.82–1.72 (m, 18 H, CH_2), 0.85 (t, 7.2 Hz, 9 H, ω-CH_3) 1.30 [s, 9 H, $(CH_3)_3$], 2.30 (s, 3 H, 2-CH_3), 2.36 (s, 3 H, 3-CH_3), 6.77 (d, J_{HH} = 6.6 Hz, Sn satellites: J_{SnH} = 33.5 Hz, 1 H, H6), 7.95 (d, J_{HH} = 6.6 Hz, Sn satellites: J_{SnH} = 6.4 Hz, 1 H, H7), 9.12 (s, 1 H, NH)

***N*-{2,3-Dimethyl-7-[(2*E*)-3-phenylprop-2-enoyl]imidazo[1,2-*a*]pyridin-8-yl}-2,2-dimethylpropanamide (2a); Typical Procedure**

To a soln of **7** (54.4 g, 87% purity, 89 mmol) in THF (0.6 L) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (1.0 g, 1.0 mmol) and LiCl (5.5 g, 130 mmol) under argon. A soln of cinnamoyl chloride (21.7 g, 130 mmol) in THF (50 mL) was added and the mixture was refluxed for 2.5 h during which time a thick yellow precipitate was formed. The mixture was stirred at r.t. overnight and the precipitate was collected and washed with Et_2O. The crude product was suspended in H_2O (0.6 L) and the pH was adjusted to pH 10 with aq 2 M NaOH. The mixture was extracted with CH_2Cl_2 (4 ×) and the combined organic phases were washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized (EtOAc–Et_2O) to give **2a** (21.9 g, 66%) as a yellow solid; mp 177–179 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12 [s, 9 H, $(CH_3)_3$], 2.38 (s, 3 H, 2-CH_3), 2.45 (s, 3 H, 3-CH_3), 7.01 (d, J_{HH} = 7.1 Hz, 1 H, H6), 7.20 (d, J_{HH} = 16.1 Hz, 1 H, PhCH=C*H*CO), 7.39–7.43 (m, 3 H, *m*-H, *p*-H), 7.45 (d, J_{HH} = 16.1 Hz, 1 H, PhC*H*=CHCO), 7.65–7.69 (m, 2 H, *o*-H), 8.13 (d, J_{HH} = 7.1 Hz, 1 H, H5), 9.50 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 8.03 (3-CH_3), 13.20 (2-CH_3), 26.95 [3 C, C(CH_3)$_3$], 38.94 [$C(CH_3)_3$], 110.62 (C6), 118.48 (C3), 120.77 (C5), 124.24 (C8), 125.23 (PhCH=*C*HCO), 126.17 (C7), 128.24 (2 C, *o*-C), 128.81 (2 C, *m*-C), 130.21 (*p*-C), 134.65 (phenyl C_q), 139.01 (C8a), 140.39 (C2), 141.71 (Ph*C*H=CHCO), 176.52 (NHC=O), 190.25 (C=O).

Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.42; H, 6.62; N, 11.20.

***N*-{7-[(2*E*)-3-(2-Chlorophenyl)prop-2-enoyl]-2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl}-2,2-dimethylpropanamide (2b)**

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.12 [s, 9 H, $(CH_3)_3$], 2.37 (s, 3 H, 2-CH_3), 2.44 (s, 3 H, 3-CH_3), 7.05 (d, J_{HH} = 7.0 Hz, 1 H, H-6), 7.30 (d, J_{HH} = 15.9 Hz, 1 H, PhCH=C*H*CO), 7.42 (m, 2 H, H_{arom}), 7.53 (m, 1 H, H_{arom}), 7.77 (d, J_{HH} = 15.9 Hz, 1 H, PhC*H*=CHCO), 7.85 (m, 1 H, H_{arom}), 8.14 (d, J_{HH} = 7.0 Hz, 1 H, H-5), 9.54 (s, 1 H, NH).

***N*-{7-[(2*E*)-3-(2,6-Dichlorophenyl)prop-2-enoyl]-2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl}-2,2-dimethylpropanamide (2c)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12 [s, 9 H, $(CH_3)_3$], 2.37 (s, 3 H, 2-CH_3), 2.45 (s, 3 H, 3-CH_3), 7.08 (d, J_{HH} = 7.0 Hz, 1 H, H-6), 7.38 (d, J_{HH} = 16.2 Hz, 1 H, PhCH=C*H*CO), 7.40 (t, J_{HH} = 8.2 Hz, 1 H, *p*-H), 7.56 (d, J_{HH} = 16.2 Hz, 1 H, PhC*H*=CHCO), 7.57 (d, J_{HH} = 8.2 Hz, 2 H, *m*-H), 8.15 (d, J_{HH} = 7.0 Hz, 1 H, H-5), 9.62 (s, 1 H, NH).

***N*-(2,3-Dimethyl-7-{(2*E*)-3-[2-(trifluoromethyl)phenyl]prop-2-enoyl}imidazo[1,2-*a*]pyridin-8-yl)-2,2-dimethylpropanamide (2d)**

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.10 [s, 9 H, $(CH_3)_3$], 2.38 (s, 3 H, 2-CH_3), 2.45 (s, 3 H, 3-CH_3), 7.01 (d, J_{HH} = 7.0 Hz, 1 H, H-6), 7.35 (d, J_{HH} = 15.6 Hz, 1 H, PhCH=C*H*CO), 7.57–7.86 (m, 4 H,

H_{arom} and PhC*H*=CHCO), 8.16 (d, J_{HH} = 7.0 Hz, 1 H, H-5), 9.53 (s, 1 H, NH).

N-{7-[(2*E*)-1-Hydroxy-3-phenylprop-2-enyl]-2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl}-2,2-dimethylpropanamide (10)

To a soln of **3** (5.0 g, 20 mmol) in anhyd Et_2O (200 mL) was added dropwise 1.5 M *t*-BuLi in pentane (40 mL, 60 mmol) at –78 °C over a period of 30 min. After a further 30 min at –78 °C, cinnamaldehyde (7.5 mL, 60 mmol) was added slowly to the suspension and stirring was continued at –78 °C for 1 h and at r.t. for 1 h. The mixture was poured into H_2O and neutralized with 6 M HCl. The mixture was extracted with EtOAc (2 ×) and the combined organic phases were washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (EtOAc) and crystallized (Et_2O) to give **10** (4.5 g, 60%) as a colorless solid; mp 195–196 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.31 [s, 9 H, $(CH_3)_3$], 2.29 (s, 3 H, 2-CH_3), 2.36 (s, 3 H, 3-CH_3), 5.41 [ddd, J_{HH} = 4.5, 4.5, 1.2 Hz, 1 H, C*H*(OH)], 5.64 (d, J_{HH} = 4.5 Hz, 1 H, OH), 6.44 (dd, J_{HH} = 16.0, 4.5 Hz, 1 H, PhCH=C*H*CO), 6.65 (dd, J_{HH} = 16.0, 1.2 Hz, 1 H, PhC*H*=CHCO), 6.96 (d, J_{HH} = 7.1 Hz, 1 H, H6), 7.16–7.24 (m, 1 H, *p*-H), 7.26–7.33 (m, 2 H, *m*-H), 7.34–7.39 (m, 2 H, *o*-H), 8.05 (d, J_{HH} = 7.1 Hz, 1 H, H5), 9.16 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.99 (3-CH_3), 13.15 (2-CH_3), 27.45 [3 C, C(*C*H_3)$_3$], 38.76 [*C*$(CH_3)_3$], 67.31 [*C*H(OH)], 109.56 (C6), 115.98 (C3), 121.59 (C8), 122.04 (C5), 126.10 (2 C, *o*-C), 127.16 (*p*-C), 127.42 (Ph*C*H=CHCO), 128.51 (2 C, *m*-C), 132.21 (PhCH=*C*HCO), 134.96 (C7), 136.83 (phenyl C_q), 138.34 (C2), 141.03 (C8a), 177.40 (C=O).

Anal. Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13. Found: C, 73.13; H, 7.34; N, 10.86.

N-{2,3-Dimethyl-7-[(2*E*)-3-phenylprop-2-enoyl]imidazo[1,2-*a*]pyridin-8-yl}-2,2-dimethylpropanamide (2a)

To a soln of **10** (93.6 g, 0.25 mol) in $CHCl_3$ (1.6 L) was added MnO_2 (282 g, 3.24 mol) and the mixture was stirred overnight at r.t. The mixture was filtered and the filtrate was evaporated. The residue was crystallized (EtOAc–Et_2O) to give **2a** (69.8 g, 75%) as a yellow solid; mp 184–186 °C.

Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.30; H, 6.81; N, 11.06.

2,3-Dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-*h*][1,7]naphthyridin-7(8*H*)-one (1a); Typical Procedure

To an ice-cold soln of **2a** (33.3 g, 88.6 mmol) in dioxane (250 mL) was slowly added concd HCl (130 mL) and the mixture was refluxed overnight. The mixture was cooled down, evaporated to a total volume of 100 mL and neutralized with concd NH_3. The resulting suspension was extracted with EtOAc (4 ×) and the combined organic phases were washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (EtOAc–light petroleum ether, 3:1) and crystallized (*i*-Pr_2O) to give **1a** (17.9 g, 69%) as a yellow solid; mp 138–140 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3 H, 2-CH_3), 2.35 (s, 3 H, 3-CH_3), 2.93 (AB, A: dd, J_{HH} = 16.3, 6.8 Hz, B: dd, J_{HH} = 16.3, 6.1 Hz, 2 H, H8), 4.99 (ddd, J_{HH} = 6.8, 6.1, 2.6 Hz, 1 H, H9), 6.95 (d, J_{HH} = 7.1 Hz, 1 H, H6), 7.21–7.27 (m, 1 H, *p*-H), 7.27–7.33 (m, 2 H, *m*-H), 7.34–7.41 (m, 2 H, *o*-H), 7.39 (d, J_{HH} = 7.1 Hz, 1 H, H5), 7.85 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.92 (3-CH_3), 12.86 (2-CH_3), 43.14 (C8), 54.51 (C9), 106.44 (C6a), 107.46 (C6), 112.26 (C5), 120.21 (C3), 126.12 (2 C, *o*-C), 127.23 (*p*-C), 128.30 (2 C, *m*-C), 134.59 (C10b), 138.83 (C2), 141.34 (2 C, C10a, phenyl C_q), 188.92 (C=O).

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 74.07; H, 5.91; N, 14.22.

9-(2-Chlorophenyl)-2,3-dimethyl-9,10-dihydroimidazo[1,2-*h*]-1,7-naphthyridin-7(8*H*)-one (1b)

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.32 (s, 3 H, 2-CH_3), 2.38 (s, 3 H, 3-CH_3), 2.90 (AB; A: dd, J_{HH} = 16.3, 6.9 Hz, B: dd, J_{HH} = 16.3, 6.4 Hz, 2 H, H-8), 5.28 (m, 1 H, H-9), 6.97 (d, J_{HH} = 7.1 Hz, 1 H, H-6), 7.22–7.50 (m, 4 H, H_{arom}), 7.46 (d, J_{HH} = 7.1 Hz, 1 H, H-5), 7.90 (s, 1 H, NH).

9-(2,6-Dichlorophenyl)-2,3-dimethyl-9,10-dihydroimidazo[1,2-*h*]-1,7-naphthyridin-7(8*H*)-one (1c)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.29 (s, 3 H, 2-CH_3), 2.36 (s, 3 H, 3-CH_3), 2.54 (ddd, J_{HH} = 16.8, 5.8, 1.1 Hz, 1 H, H-8), 3.31 (dd, J_{HH} = 16.7, 14.9 Hz, 1 H, H-8), 5.72 (dd, J_{HH} = 14.9, 5.8 Hz, 1 H, H-9), 7.03 (d, J_{HH} = 7.1 Hz, 1 H, H-6), 7.37 (m, 1 H, *p*-H), 7.43 (d, J_{HH} = 7.1 Hz, 1 H, H-5), 7.49 (m, 2 H, *m*-H), 7.93 (s, 1 H, NH).

2,3-Dimethyl-9-[2-(trifluoromethyl)phenyl]-9,10-dihydroimidazo[1,2-*h*]-1,7-naphthyridin-7(8*H*)-one (1d)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.30 (s, 3 H, 2-CH_3), 2.38 (s, 3 H, 3-CH_3), 2.82 (m, 2 H, H-8), 5.22 (t, J_{HH} = 8.1 Hz, 1 H, H-9), 7.02 (d, J_{HH} = 7.0 Hz, 1 H, H-6), 7.49 (d, J_{HH} = 7.0 Hz, 1 H, H-5), 7.53 (t, J_{HH} = 7.8 Hz, 1 H, H_{arom}), 7.68 (t, J_{HH} = 7.8 Hz, 1 H, H_{arom}), 7.74 (d, J_{HH} = 7.8 Hz, 1 H, H_{arom}), 7.83 (s, 1 H, NH), 7.89 (d, J_{HH} = 7.8 Hz, 1 H, H_{arom}).

Acknowledgment

We would like to thank Mrs. C. Schneider, Mrs. C. Hartbaum, Mr. B. Grobbel, and Mr. U. Dölling for their skillful technical assistance in the preparative work. We are also indebted to Professor R. R. Schmidt, Universität Konstanz, for numerous critical and fruitful discussions.

References

(1) For a review on DOM, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

(2) Anctil, E. J.-G.; Snieckus, V. *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**, 761–813.

(3) Simon, W.-A.; Postius, S.; Riedel, R.; Senn-Bilfinger, J.; Grundler, G. WO 9842707, **1998**.

(4) See, for example: (a) Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, *55*, 1757. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y. *J. Med. Chem.* **1998**, *41*, 1155.

(5) Blewitt, H. L. *Special Topics in Heterocyclic Chemistry*; Weissberger, A.; Tailor, E. C., Eds.; Wiley: New York, **1977**, 117.

(6) (a) Tamura, Y.; Fujita, M.; Chen, L.-C.; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564. (b) Güngör, T.; Marsais, F.; Queguiner, G. *Synthesis* **1982**, 499. (c) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.

(7) For related reactions of heterocyclic stannanes with acyl chlorides, see, for example: (a) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003. (b) Arukwe, J.; Benneche, T.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 255. (c) Buron, F.; Plé, N.; Turck, A.; Queguiner, G. *J. Org. Chem.* **2005**, *70*, 2616.

(8) For Stille cross-coupling reaction with imidazo[1,2-*a*]pyridines, see, for example: Hervet, M.; Théry, I.; Gueiffier, A.; Enguehard-Gueiffier, C. *Helv. Chim. Acta* **2003**, *86*, 3461.
(9) For a review, see, for exampl: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(10) (a) Bumagin, N. A.; Bumagina, I. G.; Kashin, A. N.; Beletskaya, I. P. *J. Org. Chem. USSR (Engl. Transl.)* **1982**, 977. (b) Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.
(11) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.
(12) (a) Senn-Bilfinger, J.; Postius, S.; Simon, W.-A.; Grundler, G.; Hanauer, G.; Huber, R.; Kromer, W.; Sturm, E. WO 0017200, **2000**. (b) Simon, W.-A.; Herrmann, M.; Klein, T.; Shin, j. M.; Huber, R.; Senn-Bilfinger, J.; Postius, S. *J. Pharmacol. Exp. Ther.* **2007**, *321 3*, 866. (c) Senn-Bilfinger, J.; Ferguson, J. R.; Holmes, M. A.; Lumbard, K. W.; Huber, R.; Zech, K.; Hummel, R.-P.; Zimmermann, P. J. *Tetrahedron Lett.* **2006**, *47*, 3321.