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An unusual rearrangement involving 5-bromo-1-phenylpyridone during its methyl cross coupling with turbo-Grignard reagent, leading to a 5-bromopyridone-fused seven-membered carbocyclic ring

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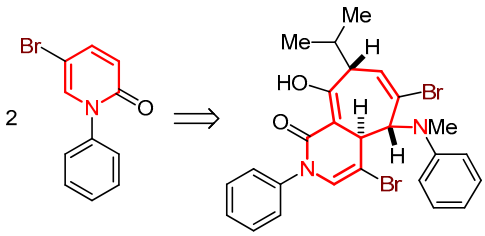
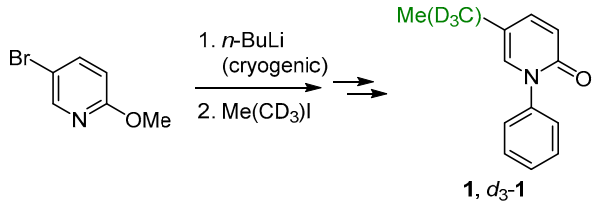


The structure of a cyclohepta[*c*]pyridin-1-one, a product of an unusual transformation, isolated during a turbo-Grignard reagent-promoted methyl cross coupling to 5-bromo-1-phenyl-2-pyridone, was determined by ^{1}H and ^{13}C NMR, COSY and high-resolution MS, as well as computer modeling. Its formation suggests a remarkable nucleophilic attack at the α-position to the pyridone carbonyl group. A rational pathway is presented.

Keywords: cyclohepta[*c*]pyridin-1-one, 3,4-dihydropyridin-2(1*H*)-one, 3-halo-1-phenylpyridone, turbo-Grignard reagent.

Dihydropyridones and piperidinones are of general interest as promising anticancer drugs[1], antiHIV[2] and potentially anti-diabetic[3] and central nervous system drugs.[4] Pirfenidone (**1**) is one of the two drugs approved to date for retarding idiopathic pulmonary fibrosis (IPF),[5] a serious, rare, and fatal lung disease. One of the pathways to compound **1**, which is applicable to the introduction of both methyl and CD_3 groups, involves conversion of 5-bromo-2-methoxypyridine to its active lithiated derivative, followed by its trapping with an electrophilic methyl reagent in a route to 5-methyl-2-pyridone and its *N*-arylated product pirfenidone (**1**), as well as to deupirfenidone (d_3-**1**) (Scheme 1)[6].

Scheme 1



In an effort to avoid the use of BuLi and low temperature conditions, we investigated non-cryogenic methylation routes, which led to a quantitative green synthesis of pirfenidone (**1**) and has been reported elsewhere.[7] We report here a unique rearrangement product resulting during our attempts to synthesize compound **1** by cross methylation of 5-bromo-1-phenylpyridin-2(1*H*)-one (**2**) using the commercially available isopropylmagnesium chloride – lithium chloride complex (*i*-PrMgCl·LiCl). This reagent, first introduced by Knochel in 2004,[8] is known as turbo-Grignard reagent and has been consistently highlighted by a number of research groups for its effectiveness under mild reaction conditions. This method also exhibits functional group tolerance and chemoselectivity during halogen–magnesium exchange. The reaction of compound **2** with turbo-Grignard at –12 to –10°C in THF, followed by an addition of 2 equiv of methyl iodide, resulted mostly in dehalogenation to "H-product" **3** along with a substantial homocoupling to 1,1'-diphenyl-3,3'-bipyridine-6,6'(1*H*,1'*H*)-dione (**4**) and only minor amounts of the desired 5-methyl-1-phenylpyridin-2(1*H*)-one (**1**) (Scheme 2, Table 1, entry 1).

Scheme 2

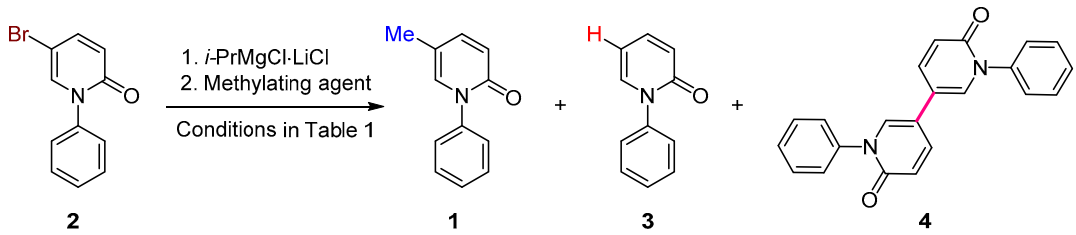


Table 1. Conditions and products of the metalation/methylation of 5-bromo-1-phenylpyridin-2(1*H*)-one (**2**)

Entry	Metalation conditions*	Methylation reagent (equiv)	Time	Distribution of products**, %		
				1	**3***[4]	**4**
1	**2** + *i*-PrMgCl·LiCl (1.15 equiv)	MeI (2)	24 h	5	80.6	13
2	**2** + *i*-PrMgCl·LiCl (1.5 equiv)	MeI (2)	4 h***	4.2	75	20
3	**2** + *i*-PrMgCl·LiCl (1.5 equiv)	TfOMe (2)	5 h	0.3	82	2.6
4	**2** + *i*-PrMgCl·LiCl (1.5 equiv)	Me_2SO_4 (2)	5 days	4	72.5	3
5*[5]	**2** + *i*-PrMgCl·LiCl (1.46 equiv) + + CuCN·2LiCl (0.1 equiv)	MeI (4)	20 h	40.8	27.6	11.8
6	**2** + *i*-PrMgCl·LiCl (1.57 equiv)	MeI (4.7)	1 h	12.8	87.2	0

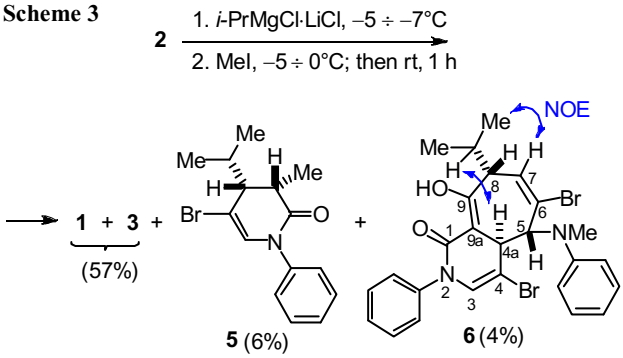
* In THF at –12 ÷ –10°C (entries 1–5) or at –5 ÷ 0°C (entry 6).
** Main products only; based on HPLC.
*** No change in the product distribution after 24 h.
*[4] As shown by TLC and HPLC, 96% of compound **3** was formed after quenching a sample of reaction mixture with water, except for entry 5.
*[5] 8.6% of the starting material **2** was detected.

Püschl et al. showed that in 5-iodo-2-methoxypyridine, *i*-PrMgCl·LiCl forms the C–metal bond very effectively and that avoiding prolonged reaction times prevents the formation of its dimer, an analog of compound **4**.[9] The organomagnesium reagent derived *in situ* from compound **2** reacted with C=O and C=N electrophiles, but not with an "electrophilic methyl". Our investigation confirmed the Püschl report regarding the kinetics of the turbo-Grignard reaction with 5-iodo-2-methoxypyridine, however, this did not lead to improved methylation of our pyridine system.

In our case, the methylation of compound **2** still produced bipyridine derivative **4** even when reaction time was shortened (Table 1, entry 2). At even shorter reaction time (and large excess of MeI) formation of compound **4** was indeed prevented, but more of compound **3** was formed (Table 1, entry 6). The presence of the dehalogenation product **3**,[10,11a] was especially bothersome, since it was almost impossible to separate it from compound **1**, even by chromatography. Replacing methyl iodide by another electrophilic methylating agent, such as methyl sulfate or methyl triflate, did not reduce the amount of "H-product" **3** as shown in Table 1 (entries 3, 4). Addition of 0.1 equiv of a less electropositive metal, such as CuCN, had attenuated the reactive magnesiate species derived from compound **2** resulting in a higher fraction of compound **1** in the distribution of products, but with a substantial amount of unreacted starting material **2** (Table 1, entry 5).

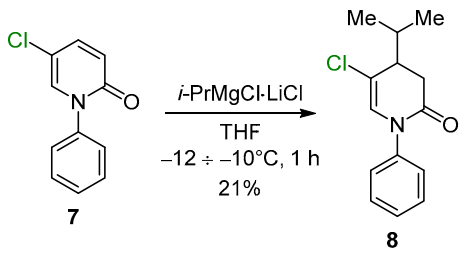
When we changed the conditions and turbo-Grignard reagent was added dropwise at –5°C to compound **2**, until its near disappearance and appearance of product **3** (as measured by HPLC in a sample from the reaction, quenched with water), and only then adding 5 equiv of MeI, two new lipophilic side products were isolated by chromatography in low yield, in addition to 57% of a mixture of "H-product" **3** and pirfenidone (**1**) (ratio of 87:13 in HPLC, Table 1, entry 6). The two lipophilic products were identified (Scheme 3) as *cis*-5-bromo-4-isopropyl-3-methyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-one (**5**) (6%) and an unusual cycloheptadienol-fused pyridone **6** (4%).

Scheme 3



In an effort to improve the yields of the lipophilic products **5** and **6**, we also examined the reaction of the turbo-Grignard reagent with the chloro analog of compound **2**, 5-chloro-1-phenylpyridin-2(1*H*)-one (**7**) (Scheme 4). The latter was prepared by Chan–Evans–Lam *N*-phenylation[11a] of 5-chloropyridone. However, the reaction of compound **7** with turbo-Grignard reagent proceeded in a different manner than the reaction of its bromo analog **1**, affording

Scheme 4



only 5-chloro-4-isopropyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-one **8** in 21% yield, in addition to recovered starting material **7**. The structures of compounds **5**, **6**, and **8** were established conclusively by ^{1}H and ^{13}C NMR, ^{1}H–^{1}H COSY, as well as by high-resolution MS.

Formation of products **5** and **8** can be readily explained as the result of 1,4-addition of *i*-PrMgCl (from the turbo-Grignard reagent), followed, in the case of compound **5**, by trapping the resulting enolate by methylation at position 3 of the pyridone system. In fact, Sośnicki et al.[11b,c] in extensive studies has shown that magnesium metalate complexes ($RMgR'_2$ + LiCl), formed from RMgCl and BuLi or MeLi in a 1:2 molar ratio at 0°C in THF solution, react in cryogenic conditions with *N*-phenyl-,[11b] or *N*-allyl-,[11c] or *N*-benzyl-2-pyridones[11c] both by 1,4- and 1,6-addition of an allyl, and even vinyl group to furnish the respective 4- or 6-allyldihydropyridones with 1,6-regioselectivity for the vinyl addition.[11b] It should be pointed out that no other examples of the addition of magnesiates or Grignard reagents to pyridin-2(1*H*)-ones have so far been reported.

The NMR spectrum of compound **8** clearly indicates that the isopropyl group is pseudo-equatorial, apparently due to a half chair conformation of the dihydropyridone. As a consequence, the proton 4-CH (signal at 2.53 ppm) adjacent to the isopropyl group has two very different coupling constants with the protons of the adjacent methylene: ^{3}J = 8.5 Hz with the proton at 2.96 ppm (an approximately diaxial arrangement) and ^{3}J = 2.5 Hz with the proton at 2.72 ppm (a gauche relationship). Interestingly, in compound **5** the methyl and isopropyl groups are *cis*-oriented, as indicated by the 1 Hz vicinal coupling constant between the ring protons at 2.23 and 2.78 ppm. The enolate resulting from Michael addition of *i*-PrMgCl and containing a pseudo-equatorial *i*-Pr group apparently prefers, due to stereoelectronic reasons, to form a *pseudo*-axial bond with the methyl electrophile, thus leading to the *cis*-isopropyl–methyl stereochemistry (Scheme 3).

Structure **6**, which is apparently constructed from two bromopyridone units of compound **2**, with the addition of an isopropyl group and a methyl group, the latter being the result of *N*-methylation, was unequivocally established by high-resolution MS and ^{13}C and ^{1}H 1D NMR spectra, as well as several 2D techniques (^{1}H –^{1}H COSY, ^{1}H –^{1}H NOESY, ^{1}H –^{13}C HMQC, and ^{1}H –^{13}C HMBC). ^{15}N NMR chemical shifts were obtained from a 2D ^{1}H–^{15}N HMBC correlation spectrum and also indicate *N*-methylation. For the determination of the stereochemistry, a molecular mechanics calculation (PCModel, Serena Software, Scheme 3 and Fig. 1) was instrumental, together with the

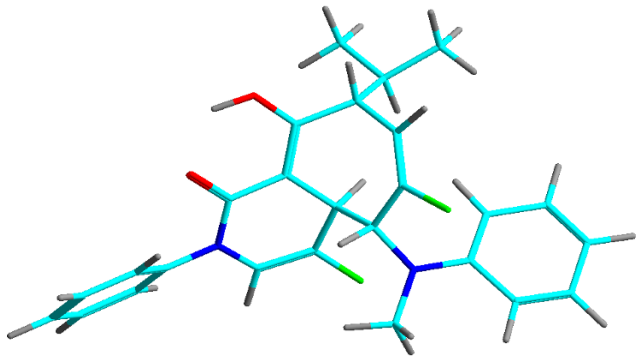


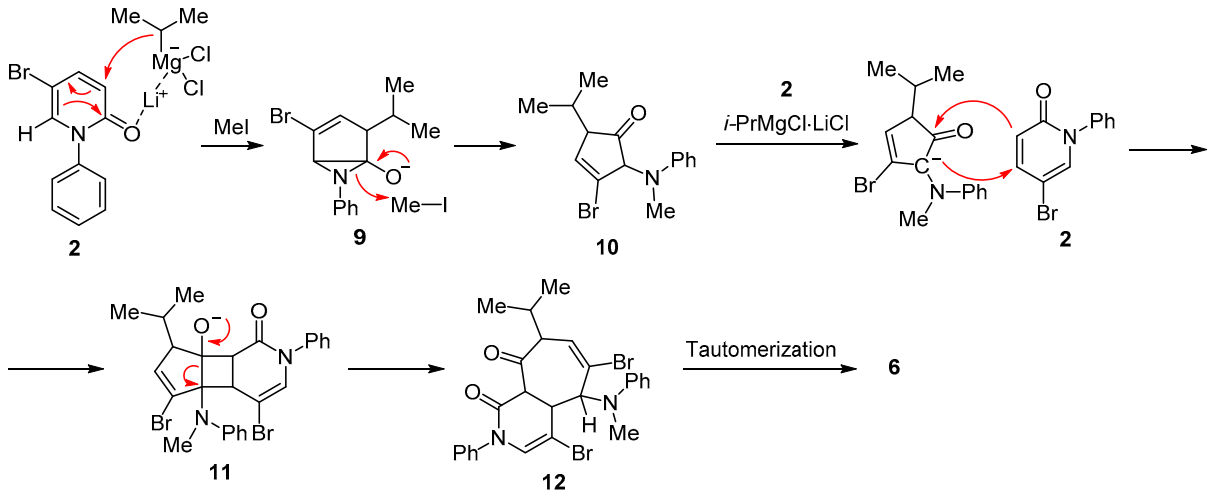
Figure 1. Molecular mechanics-calculated stereostructure for compound **6**.

observation of a few nontrivial NOE interactions. ^{1}H NMR spectra clearly shows the 8-CH proton (2.59 ppm) coupled to the CH proton of the isopropyl group, as well as to the vinylic 7-CH proton. The 4a, 5-CH protons (4.31 and 4.83 ppm, respectively) constitute an *anti* arrangement, as indicated by their large coupling constant (^{3}J = 11 Hz), but weak NOE interaction. Especially diagnostic is a strong NOE (1,6-interaction!) between the bridgehead 4a-CH proton (4.31 ppm) and CH proton of the isopropyl group (2.34 ppm). In the calculated conformation, these two protons are only 2.0 Å from each other, with the 4a-CH proton pointing into the concave side of the 7-membered ring and the isopropyl CH pointing inwards, while both methyl groups point away. At the same time, the 8-CH proton is pointing out on the convex side, as is the 5-CH proton. For the same reason, one of the isopropyl methyl groups (at 1.16 ppm), but not the other one (1.11 ppm) has a measurable NOE with the adjacent olefinic 7-CH proton (6.55 ppm). The PCModel calculations (Fig. 1) further indicate hydrogen bonding between the enolic OH proton and the carbonyl group oxygen.

Formation of compound **6**, a 5-bromo-*N*-phenylpyridone fused to a seven-membered ring, with preservation of the two bromine substituents, though only a minor product, is most intriguing and, to the best of our knowledge, unprecedented. Sośnicki[11b] showed that a chlorine substituent can survive during 1,6-additions of vinyl magnesium metalate complexes to pyridones, but substitution at the α-position to the lactam carbonyl had not been observed. In our case, isopropyl metalate reagents led to isolation of pirfenidone (**1**), but no formation of compounds **5** or **6** was detected.[7] At first glance, the introduction of an isopropyl group into compound **6** is reminiscent of formation of the two other side products **5** and **8**. However, while the two latter compounds are products of 1,4-addition of *i*-PrMgCl·LiCl to the conjugated carbonyl of the pyridone, resulting in the isopropyl group being in the β-position to the C=O group, the placement of the isopropyl substituent in the corresponding α-position in compound **6** is indicative of a more complicated transformation.

The mechanism of formation of compound **6** is still unclear, but a plausible pathway of this unusual transformation is depicted in Scheme 5. The first step, which takes into account the placement of the isopropyl substituent at

Scheme 5



the α-position to the carbonyl group in compound **6**, involves coordination of *i*-PrMgCl·LiCl with the carbonyl oxygen. This increases the electrophilicity of the carbonyl carbon and is followed by a nucleophilic attack of *i*-PrMg at the α-position in respect to the lactam C=O group, leading to the azabicyclo[3.1.0]hexene intermediate **9**. The latter can be expected to undergo rapid ring opening due to relief of strain in the unstable aziridinol anion, with concurrent *N*-methylation leading to the cyclopentenone **10**. Next, the formation of a 7-member ring can be the result of collapse of a hydroxylated azatricyclo[4.2.0]-undecane intermediate **11**, which itself is formed by Michael addition of the enolate of ketone **10** (resulting from deprotonation by the basic Grignard reagent) onto a small amount of still unreacted pyridone **2**. This would lead to formation of diketone **12**, the keto form of product **6**.

To conclude, reaction of 5-chloro- or 5-bromo-1-phenyl-pyridone with the turbo-Grignard, an attenuated Grignard reagent, leads to 1,4-addition of an isopropyl group and isolation of the corresponding 5-halo-4-isopropyldihydro-pyridones possessing a half-chair conformation, as indicated by NMR spectra. Furthermore, in the case of 5-bromo-1-phenylpyridone, an unusual side product, comprising a seven-membered ring fused to a 5-bromo-2-dihydropyridone moiety, was isolated, the structure of which indicates an unprecedented attack of the Grignard reagent at the α-position to the pyridone carbonyl group. It is hoped that these unusual transformations, though only occurring in low yield, will stimulate further research and optimization toward the synthesis of functionalized dihydropyridones and piperidinones, some of which can be found in biologically active compounds and drugs.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments: Avance-III-700 (700 and 176 MHz, respectively), DMX-600 (600 and 150 MHz, respectively), and Avance-400 (400 and 100 MHz, respectively). To all solutions, TMS was added as an internal standard. Series of 2D spectra were also obtained for compounds **4**–**6** and **8** (NOESY mixing time 1.5 s), which allowed the full attribution of all carbon and proton signals. ^{15}N chemical shifts were indirectly obtained from ^{1}H–^{15}N HMBC spectra (run on the Avance-III-700 instrument; ^{15}N frequency 71.0 MHz). High-resolution mass spectra were obtained on an Agilent 6545 QTOF (ESI) instrument integrated with an Agilent 1260 UPLC apparatus. Mass spectra were obtained on an Agilent SQ 6120 (ESI). Progress of the reactions was monitored by thin-layer chromatography (mobile phase hexane–AcOEt, 1:4) on silica gel (60F, Merck Art. 5554), with visualization of the TLC plates using ultraviolet light, and by HPLC using a Shimadzu chromatograph equipped with an Agilent eclipse XDB-C18 column (5 μ, 4.6 ×150 mm) using mobile phase where solution A was 0.02% aqueous TFA and solution B was 0.02% TFA in MeCN with a gradient from 95% of solution A and 5% of solution B (*t* 0 min) to 30% A and 70% B (*t* 20 min), flow rate 1 ml/min, run time 25 min, UV detection at 220 nm, column temperature was 35°C, injection volume 10 μl. Flash chromatography was carried out using Combi-Flash in Redi*Sep*® Rf disposable, bare silica (40–63 μ, 230–400 mesh) columns (24 g) where the mobile phase was a gradient of EtOAc (0–75%) in hexane.

1,1'-Diphenyl-3,3'-bipyridine-6,6'(1*H*,1'*H*)-dione (4). Compound **2**[7] (1.0 g, 4.0 mmol) was dissolved in THF (extra dry, 20 ml), and the solution was cooled to –12 ÷ –10°C under N_2. The turbo-Grignard reagent (*i*-PrMgCl·LiCl, 1.3 M in THF, 4.5 ml, 5.85 mmol, 1.46 equiv) was added dropwise. After the addition, TLC indicated formation of compound **3** (in a sample of the reaction mixture quenched with water) and disappearance of the starting material **2** (about 4% of compound **2** could be detected by HPLC). CuCN·2LiCl (1 M solution in THF, 0.4 ml, 0.1 equiv) was added, and the reaction mixture was stirred at –12 ÷ –10°C for 15 min followed by addition of MeI (2.28 g, 16 mmol, 4 equiv). The reaction was monitored for 20 h by HPLC which showed the formation of products **1** (40.8%), **3** (27.6%), and **4** (11.8%). Compound **4** was isolated by flash chromatography as a white solid. Yield 0.136 g (10%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz):

7.97 (2H, d, J = 2.0, H-2 Py); 7.86 (2H, dd, J = 9.5, J = 2.0, H-4 Py); 7.53–7.42 (10H, m, H Ph), 6.54 (2H, d, J = 9.5, H-5 Py). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 160.3 (C=O); 140.7 (C-1 Ph); 139.3 (C-4 Py); 135.2 (C-2 Py); 128.9, 128.1, 126.9 (C-2,3,4,5,6 Ph); 120.5 (C-5 Py); 114.3 (C-3 Py). Found, *m*/*z*: 363.1108 $[M+Na]^+$. $C_{22}H_{16}N_2NaO_2$. Calculated, *m*/*z* 363.1104.

Reaction of compound 2 with the turbo-Grignard reagent under the rearrangement conditions. Compound **2** (2.08 g, 8.3 mmol) was dissolved in THF (40 ml) under N_2 and the solution was cooled to –5 ÷ –7°C, and the turbo-Grignard reagent (*i*-PrMgCl·LiCl, 1.3 M in THF, 10 ml, 13 mmol, 1.57 equiv) was added dropwise, after which TLC clearly showed formation of compound **3** (in a sample of the reaction mixture quenched with water) and disappearance of the starting material **2** (about 4% of compound **2** could be detected in the HPLC). MeI (5.6 g, 2.46 ml, 39 mmol, 4.7 equiv) was added at –5 ÷ 0°C, after which the mixture was allowed to reach room temperature and was further stirred for 1 h at room temperature. Then the reaction was quenched with water (30 ml) and extracted with EtOAc (20 ml), the organic phase was separated; the aqueous phase was washed with EtOAc (20 ml), and the combined organic phase was dried over Na_2SO_4, filtered, and evaporated to leave a residue which was purified by chromatography to obtain 0.85 g (57%) of a mixture of compounds **1** and **3** (12.8/87.2%, HPLC), 150 mg (6%) of compound **5**, and 87 mg (4%) of compound **6**.

5-Bromo-4-isopropyl-3-methyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-one (5). Brown oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.42–7.36 (2H, m, H Ph); 7.31–7.25 (1H, m, H Ph); 7.22–7.18 (2H, m, H Ph); 6.61 (1H, s, H-6); 2.78 (1H, qd, J = 7.0, J = 1.0, H-3); 2.23 (1H, dd, J = 4.0, J = 1.0, H-4); 2.15–2.06 (1H, m, C<u>H</u>$(CH_3)_2$), 1.44 (3H, d, J = 7.0, 3-CH_3); 1.05 (3H, d, J = 7.0) and 0.97 (3H, d, J = 7.0, CH(C<u>H</u>$_3)_2$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 171.5 (C=O); 139.9 (C-1 Ph); 129.8 (C-6); 129.3, 127.6, 126.0 (C-2,3,4,5,6 Ph); 105.1 (C-5); 55.3 (C-4); 39.3 (C-3); 30.5 (<u>C</u>H$(CH_3)_2$); 19.9, 18.9 (CH(<u>C</u>$H_3)_2$); 18.0 (3-CH_3). Found, *m*/*z*: 308.0664 $[M+H]^+$. $C_{15}H_{19}BrNO$. Calculated, *m*/*z*: 308.0644.

4,6-Dibromo-9-hydroxy-8-isopropyl-5-[methyl(phenyl)-amino]-2-phenyl-2,4a,5,8-tetrahydro-1*H*-cyclohepta[*c*]-pyridin-1-one (6). Grayish semi-solid. ^{1}H NMR spectrum (700 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 14.93 (1H, s, OH); 7.46 (2H, t, J = 8, H-3,5 2-Ph); 7.37 (1H, t, J = 8.0, H-4 2-Ph); 7.33 (2H, d, J = 8.0, H-2,6 2-Ph); 7.25 (2H, t, J = 8.0, H-3,5 Ph); 6.84 (2H, d, J = 8.0, H-2,6 Ph); 6.75 (1H, t, J = 8.0, H-4 Ph); 6.553 (1H, s, 3-CH); 6.550 (1H, dd, J = 10.0, J = 1.5, 7-CH); 4.83 (1H, d, J = 11.0, 5-CH); 4.31 (1H, d, J = 11.0, 4a-CH); 2.87 (3H, s, NCH_3); 2.59 (1H, t, J = 10.5, 8-CH); 2.34 (1H, d, septet, J = 11.0, J = 6.5, C<u>H</u>$(CH_3)_2$); 1.16 (3H, d, J = 6.0) and 1.11 (3H, d, J = 6.0, CH(C<u>H</u>$_3)_2$). ^{13}C NMR spectrum (176 MHz, $CDCl_3$), δ, ppm: 182.7 (COH); 168.2 (C=O); 149.9 C-1 Ph); 139.0 (C-1 2-Ph); 133.6 (C-7); 131.3 (C-4); 129.4 (C-3,5 2-Ph); 129.04 (C-6); 128.98 (C-3,5 Ph); 128.0 (C-4 2-Ph); 126.3 (C-2,6 2-Ph); 117.8 (C-4 Ph); 112.2 (C-2,6 Ph); 100.2 (C-3); 94.4 (C-9a); 65.2 (C-5); 56.2 (C-8); 41.8 (C-4a); 32.9 (<u>C</u>H$(CH_3)_2$); 32.3 (NCH_3); 22.0, 21.9 (CH(<u>C</u>$H_3)_2$). Found, *m*/*z*: 557.04289 $[M+H]^+$. $C_{26}H_{27}Br_2N_2O_2$. Calculated, *m*/*z*: 557.0433.

5-Chloro-1-phenylpyridin-2(1*H*)-one (7). 5-Chloropyridin-2(1*H*)-one (9 g, 0.07 mol), phenyl boronic acid (21.3 g, 0.175 mol, 2.5 equiv), $Cu(OAc)_2 \cdot H_2O$ (13.9 g, 0.07 mol, 1 equiv), and pyridine (22 g, 0.28 mol, 4 equiv) were stirred in CH_2Cl_2 (500 ml) with constant bubbling of air through the mixture at room temperature for 24 h. After this time, TLC indicated complete consumption of the starting material. The mixture was then filtered and washed with 1 N HCl (300 ml), water (300 ml), 1 N NaOH (300 ml), and water again followed by washing with brine. The organic phase was separated and dried (Na_2SO_4). Activated charcoal (5 g) was added, and the mixture was stirred for 0.5 h, then filtered through Na_2SO_4 and activated carbon. The solvent was evaporated to leave an oil which upon further drying under vacuum (2 bar) solidified (14.5 g). This solid was dissolved in diisopropyl ether (87 ml) at reflux, and the green solution was slowly cooled to 17°C, resulting in precipitation of a solid which was filtered, washed with cold ether, and dried under vacuum to furnish product **7**. Yield 10.8 g (75%), off-white solid. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.52–7.48 (2H, m, H-3,5 Ph); 7.45–7.43 (1H, m, H-4 Ph), 7.40 (1H, dd, J = 3.0, J = 0.5, H-6); 7.38–7.36 (2H, m, H-2,6 Ph); 7.35 (1H, dd, J = 9.0, J = 3.0, H-4); 6.63 (1H, d, J = 9.0, H-3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 160.7; 140.8; 140.2; 135.4; 129.5; 128.9; 126.4; 122.7; 112.4. Mass spectrum, *m*/*z*: 206 $[M+H]^+$.

5-Chloro-4-isopropyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-one (8). Compound **7** (0.82 g, 4 mmol) was dissolved in THF (16 ml), and the solution was cooled to –15 ÷ –10°C. The turbo-Grignard reagent (*i*-PrMgCl·LiCl, 1.3 M in THF, 4.5 ml, 5.85 mmol, 1.5 equiv) was added dropwise within 15 min. The mixture was stirred at –12 ÷ –10°C for 15 min, after which TLC (against the standard of compound **3**) indicated that instead of the magnesium complex of compound **7**, a new product was formed (with substantial amount of compound **7** remaining). The reaction was therefore quenched with water and extracted with EtOAc. The organic extract was dried, filtered, and evaporated to leave a residue which was subjected to chromatographic separation of product **8** isolated as a brownish semi-solid. Yield 0.21 g (21%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.42–7.36 (2H, m, H-3,5 Ph); 7.30–7.26 (1H, m, H-4 Ph); 7.24–7.20 (2H, m, H-2,6 Ph); 6.51 (1H, s, 6-CH); 2.96 (1H, dd, J = 16.5, J = 8.5) and 2.72 (1H, dd, J = 16.5, J = 2.5, 3-CH_2); 2.53 (1H, ddd, J = 8.5, J = 4.5, J = 2.5, 4-CH); 2.15 (1H, septet, d, J = 7.0, J = 4.5, C<u>H</u>$(CH_3)_2$); 1.04 (3H, d, J = 7.0) and 1.00 (3H, d, J = 7.0, CH(C<u>H</u>$_3)_2$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 167.6 (C=O); 139.9 (C-1 Ph); 129.3 (C-3,5 Ph); 128.3 (C-6); 127.5 (C-4 Ph); 125.9 (C-2,6 Ph); 117.8 (C-5); 45.3 (C-4); 34.1 (C-3); 30.0 (<u>C</u>H$(CH_3)_2$); 19.9, 17.9 (CH(<u>C</u>$H_3)_2$). Found, *m*/*z*: 250.0993 $[M+H]^+$. $C_{14}H_{17}ClNO$. Calculated, *m*/*z*: 250.0993.

Supplementary information file, containing NMR spectra of the synthesized compounds, is available at the journal website at http://link.springer.com/journal/10593.

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