Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6559

www.rsc.org/obc

PAPER

Suzuki–Miyaura cross-coupling reactions of halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones†

Annamária Molnár,[a,b] Anita Kapros,[b] László Párkányi,[c] Zoltán Mucsi,[b] Gábor Vlád[a] and István Hermecz*[d]

Received 31st March 2011, Accepted 23rd June 2011
DOI: 10.1039/c1ob05505d

The palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with (het)arylboronic acids allow easy access to (het)aryl and vinyl derivatives of this bicycle in good to excellent yields, even from chloro derivatives. The sequence of reactivity of the halogen in the different positions of the ring system was also investigated. 6-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one could be prepared by thermal cyclization of isopropylidene (6-phenylpyrid-2-ylamino)methylenemalonate, together with a small amount of 7-phenyl-1,4-dihydro-1,8-naphthyridin-4-one.

The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one scaffold is a privileged structure[1] in medicinal chemistry, as the physical properties of its derivatives usually meet the criteria of the "rule of five" for the development of orally active drugs.[2] The derivatives display diverse biological activities, and some outstanding representatives have been introduced into human therapy as analgesic, anti-inflammatory, antiallergic or antipsychotic agents.[3] Risperidone, a member of this class, was one of the drugs most widely prescribed worldwide in 2007.[4] Paliperidone,[5] the main metabolite of risperidone, was recently introduced into human therapy as an oral atypical antipsychotic for the treatment of bipolar disorders. Its palmitate ester prodrug is currently under evaluation by the FDA as a monthly injection for the treatment of schizophrenia.[6]

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones are usually synthesized from 2-aminopyridines, and functionalization of this bicyclic ring system has not been explored, expect in positions 2 and 3.[7] Direct synthesis from 2-aminopyridines is sometimes accompanied by poor yields. For example, the potent glycogen synthase kinase 3β inhibitor 2-(4-pyridyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones could be prepared in yields of only 10–28% in the reactions of 2-aminopyridines and ethyl 3-(4-pyridyl)-3-oxopropionate in PPA at 140–150 °C for 12 h.[8]

Palladium-catalyzed cross-coupling processes for carbon–carbon bond formation of (het)aryl halides have become an indispensable tool[9] for synthetic and medicinal chemists in their search for new derivatives with wide-ranging therapeutic potential. Their industrial importance is continuously increasing.[10] The reactivities of the halo and pseudohalo derivatives of a broad range of heterocycles are studied in cross-coupling reactions.[11] One of the most widely-used methods is the Suzuki–Miyaura reaction, a powerful means with which to generate carbon–carbon bonds *via* the palladium-catalyzed cross-coupling of electrophiles with organoboranes.[12]

There has as yet been no systematic investigation of the Suzuki–Miyaura coupling of halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. Merely a few examples are to be found of the introduction of an aryl substituent into positions of 2,[13] 3,[14] 7[15] and 9[16] of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one by the Suzuki–Miyaura cross-coupling reaction. In most cases, $Pd(PPh_3)_4$ (3–5 mol%) was applied as catalyst and Na_2CO_3 as base in different solvents (most frequently DME or THF). The reaction period usually ranges from 3 h to 16 h.

Results and discussion

The present article furnishes an account of our investigations of the sequence of reactivity of chloro, bromo and iodo substituents at different positions[17] on the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton in Suzuki–Miyaura cross-coupling reactions. Preparative experiments were also performed.

It has been demonstrated that the reactivity in the palladium-catalyzed cross-coupling reactions of heterocycles is mainly determined by the relative ease of oxidative addition.[18] Handy and Zhang proposed a simple guide for predicting the sequence of coupling (*e.g.* Suzuki) in polyheteroaromatics, based upon the ^{1}H NMR chemical shifts of the parent non-halogenated heteroaromatics.[19] Whilst there are exceptions, this appears to

[a]*Chemical Development, R&D, Chinoin Ltd, Tó utca 1-5, H-1045 Budapest, Hungary*
[b]*Department of Organic Chemistry & Technology, Budapest University of Technology and Economics, Budafoki út 8, H-1111 Budapest, Hungary*
[c]*Institute of Structural Chemistry, Chemical Research Center, Hungarian Academy of Sciences, Pusztaszeri út 59, H-1025 Budapest, Hungary*
[d]*External Pharmaceutical Department, Budapest University of Technology and Economics, R&D, Chinoin Ltd, Tó utca 1-5, H-1045 Budapest*

† Electronic supplementary information (ESI) available: Protocol for Suzuki–Miyaura cross-couplings and analytical and ^{1}H and ^{13}C NMR data for compounds **29**–**44**. Cartesian coordinates of the optimized ground state energy of compound **48**. X-ray data for compound **48** (CIF). CCDC reference number 816421. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05505d

Table 1 Suzuki–Miyaura reactions of chloro derivatives **1–5** of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with phenylboronic acid **6**

Entry	Chloro deriv.	Positionof Cl	Reaction period	Ph deriv.	HPLC yield of Ph deriv.	Starting Cl compd.	Reaction period	HPLC yield of Ph deriv.
1	**1**	2	4 h	**7**	>99%	<1%	1 h	87%
2	**2**	3	4 h	**8**	55%	~43%		
3	**3**	7	4 h	**9**	67%	~33%		
4	**4**	8	4 h	**10**	>99%	<1%	1 h	94%
5	**5**	9	4 h	**11**	77%	~21%		

Table 2 Suzuki–Miyaura reactions of monohalogen derivatives **1–5** and **13–19** of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with phenylboronic acid **6** during 4 h at 80 °C

	4*H*-Pyrido[1,2-*a*]pyrimidin-4-one						
Entry	Compd.	X	Compd.	Ph position	HPLC yield	Starting halo derivative	Side-product **12**
1	**1**	2-Cl	**7**	2	>99%	<1%	<1%
2	**2**	3-Cl	**8**	3	55%	43%	2%
3	**13**	3-Br	**8**	3	73%	25%	2%
4	**17**	3-I	**8**	3	89%	<1%	11%
5	**3**	7-Cl	**9**	7	67%	33%	<1%
6	**14**	7-Br	**9**	7	>99%	<1%	<1%
7	**18**	7-I	**9**	7	91%	<1%	9%
8	**4**	8-Cl	**10**	8	>99%	<1%	<1%
9	**15**	8-Br	**10**	8	>99%	<1%	<1%
10	**5**	9-Cl	**11**	9	77%	21%	2%
11	**16**	9-Br	**11**	9	98%	<1%	2%
12	**19**	9-I	**11**	9	98%	<1%	2%

be very useful in practice, particularly in the pharmaceutical industry.[20]

On this basis, the expected reaction sequence for the chloro derivatives **1–5** of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, for example is as follows:

position 2 (8.31 ppm) > 8 (7.97 ppm) > 9 (7.70 ppm) > 7 (7.30 ppm) > 3 (6.34 ppm)

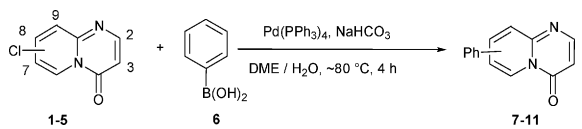
The chemical shift of 6-H (8.96 ppm) does not help as it is influenced by the anisotropic effect of the neighboring C4═O group.[21] We were interested in whether the practical rule of Handy and Zhang is applicable in our case, as a reversal of the reactivity sequence may be observed when the ^{1}H NMR chemical shifts of any two positions are within 0.2–0.3 ppm.

For the selection of a solvent and a catalyst [5 mol% $PdCl_2$ or $Pd(PPh_3)_4$], we performed preliminary investigations on the reaction of 3-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with phenylboronic acid to yield the 3-phenyl derivative in the presence of $NaHCO_3$. Hydrodebromination was a significant side-reaction (5–11%) in the presence of $PdCl_2$ as catalyst in EtOH or DME. It was also pronounced (8%) in NMP when $Pd(PPh_3)_4$ was used as catalyst, and the reaction was slower than in DME. For more detailed experiments, we finally chose $Pd(PPh_3)_4$ as catalyst and DME as solvent.

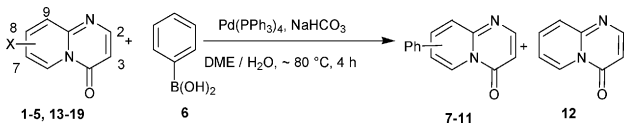
As general conditions for coupling, we used a 5% excess of the boronic acid with the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in the presence of 5% freshly prepared[22] $Pd(PPh_3)_4$ as catalyst. We applied an aqueous solution of a weak base, $NaHCO_3$, as the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton is sensitive to nucleophilic ring opening.[23] Two equivalents of $NaHCO_3$ were used relative to the boronic acid.

We investigated the conversion of chloro derivatives **1–5** with phenylboronic acid **6** after 4 h by HPLC (Table 1). In the cases of the 2-chloro (**1**) and 8-chloro (**4**) derivatives, the conversions were over 99%, and we therefore repeated the reactions with a shorter reaction period, 1 h. The reactivity sequence was predicted fairly well by the rule of Handy and Zhang, as only a reversal of the sequence for positions 2 and 8 was observed:

$$8 \geq 2 > 9 > 7 > 3$$



We next investigated the reactivities of different halogens at different positions of the bicyclic ring system, using compounds **1–5** and **13–19** with phenylboronic acid **6** (Table 2). The reaction period was 4 h and the conversion was again checked by HPLC. The sequence of reactivity of the halogens was in harmony with that expected:[24] I > Br > Cl.



The coupling reactions were accompanied by different extents of hydrodehalogenation to give unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **12**. Hydrodehalogenation was most marked for the compounds with the halogen in position 3, and especially for the iodo derivative **17**. We did not detect any homocoupled products.

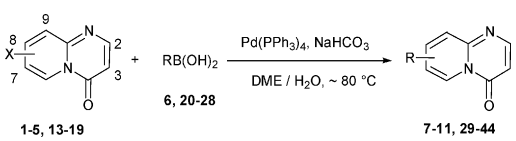
We carried out preparative experiments, too (Table 3). The reaction conditions were not optimized. We used reaction periods of 1 h (for iodo derivatives), 4 h, 24 h, 48 h and 96 h. The

Table 3 Suzuki–Miyaura reactions of monohalogen derivatives **1–5** and **13–19** of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with boronic acids **6** and **20–28**

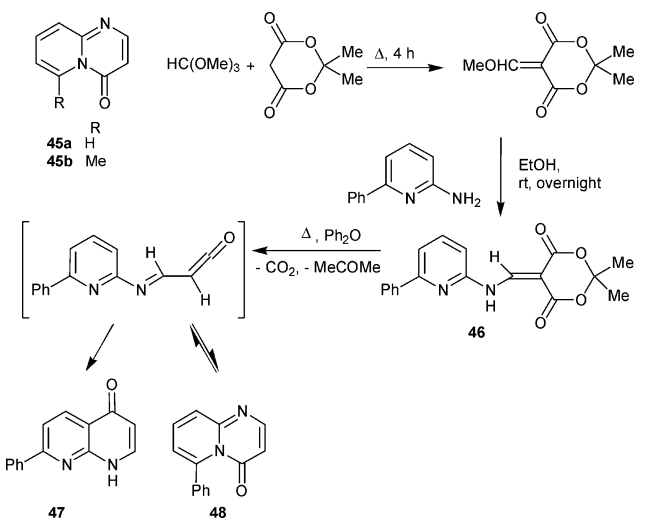
				Substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones				
Entry	Compd.	X	Boronic acid	R	Position	Compd.	Reaction time	Isolated yield
1	**1**	2-Cl	**6**	Ph	2	**7**	4 h	91%
2	**1**	2-Cl	**20**	4-MeOPh	2	29	4 h	97%
3	**1**	2-Cl	**21**	4-F_3CPh	2	**30**	4 h	91%
4	**1**	2-Cl	**22**	2-AcPh	2	**31**	24 h	85%
5	**1**	2-Cl	**23**	1-naphthyl	2	**32**	4 h	93%
6	**1**	2-Cl	**24**	3-thienyl	2	**33**	24 h	81%
7	**1**	2-Cl	**25**	3-pyridyl	2	**34**	96 h	87%
8	**1**	2-Cl	**26**	4-pyridyl	2	**35**	96 h	77%
9	**1**	2-Cl	**27**	1-pentenyl	2	**36**	24 h	99%
10	**1**	2-Cl	**28**[a]	CH_2Ph	2	**37**	96 h	38%[b]
11	**2**	3-Cl	**6**	Ph	3	**8**	48 h	98%
12	**2**	3-Cl	**20**	4-MeOPh	3	**38**	72 h	92%
13	**2**	3-Cl	**21**	4-F_3CPh	3	**39**	96 h	76%
14	**13**	3-Br	**6**	Ph	3	**8**	24 h	70%
15	**17**	3-I	**6**	Ph	3	**8**	24h	73%
16	**3**	7-Cl	**6**	Ph	7	**9**	24 h	92%
17	**3**	7-Cl	**23**	1-naphthyl	7	**40**	24 h	90%
18	**3**	7-Cl	**24**	3-thienyl	7	**41**	96 h	51%
19	**3**	7-Cl	**26**	4-pyridyl	7	**42**	96 h	89%
20	**14**	7-Br	**6**	Ph	7	**9**	4 h	91%
21	**18**	7-I	**6**	Ph	7	**9**	4 h	87%
22	**4**	8-Cl	**6**	Ph	8	**10**	4 h	97%
23	**15**	8-Br	**6**	Ph	8	**10**	4 h	92%
24	**15**	8-Br	**20**	4-MeOPh	8	**43**	4 h	81%
25	**4**	8-Cl	**27**	1-pentenyl	8	**44**	24 h	87%
26	**5**	9-Cl	**6**	Ph	9	**11**	24 h	82%
27	**16**	9-Br	**6**	Ph	9	**11**	4 h	95%
28	**19**	9-I	**6**	Ph	9	**11**	4 h	89%

[a] Benzylboronic acid pinacol ester was used. [b] The conversion was 74%. >99% conversion was achieved when Pd(dppf)Cl_2 was used as catalyst under similar reaction conditions.

longest reaction period (96 h) was necessary in the cases of the electron-deficient pyridylboronic acids **25** and **26**. The products were isolated by column/flash chromatography. The substituents on the phenyl ring of the arylboronic acids had little effect on the reaction. The isolated yields were good to excellent (70–99%), even in the case of chloro derivatives **1–5**. Chloro derivatives are usually more easily available at lower cost and they provide wider diversity than other halo derivatives.[25] It might be expected that the reaction periods and reaction temperature could be decreased by applying more electron-rich and/or σ-donating bulky phosphines,[26] *N*-heterocyclic carbene[27] ligands, or more effective palladium catalysts,[28] especially palladacycles,[28b] under microwave conditions.[29] Pentenylboronic acid **27** also provided acceptable yields (Entries 9 and 25 in Table 3). In spite of the promising conversion when pinacol borane **28** was used, 2-benzyl derivative **37** could be isolated in only moderate yield, as it was necessary to repeat the chromatographic step to obtain the compound in pure form.



It was of interest to consider whether the missing 6-phenyl derivative **48** could be obtained by thermal cyclization of pyridylaminomethylenemalonate **46**, prepared in a one-pot reaction of Meldrum's acid, trimethyl orthoformate and 6-phenyl-2-aminopyridine (Scheme 1), as the synthetic accessibility of 6-halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one is very limited.[30]



Scheme 1 Thermal cyclization of (6-phenylpyridin-2-ylamino)-methylenemalonate (**46**)in diphenyl oxide.

Thermal cyclization of (6-substituted pyridin-2-ylamino)methylenemalonates, *e.g.* **46**, may lead to the formation of kinetically controlled 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, *e.g.* **48**, and/or the thermodynamically more stable 1,4-dihydro-1,8-naphthyridin-4-ones, *e.g.* **47**, depending on the steric and

Table 4 Ground-state geometry of some 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **45a,b** and **48**, calculated DFT by B3LYP/6-311++G(2d,2p) level, and some selected geometrical data determined by single-crystal X-ray determination

	6-R	N5–C4 bond length (pm)	C6–R bond length (pm)	N5–N6–R angle (deg)	C4–N5–C6 angle (deg)	Distance between O and R (pm)	O═C4···C6–R torsion angle (deg)
45a	H	146.5	107.8	113.8	116.9	222.4	0.01
45b	Me	147.2	150.5	122.2	120.8	263.6	15.2
45b[a]	Me	*145.0(3)*	*150.4(3)*	*121.7(2)*	*121.1(2)*	*262.2*	*11.9*
48	Ph	147.3	148.5	121.5	120.1	267.7	28.2
48[a]	Ph	*145.7(2)*	*148.6(2)*	*120.6(1)*	*120.6(1)*	*268.6(2)*	*31.0(2)*

[a] measured

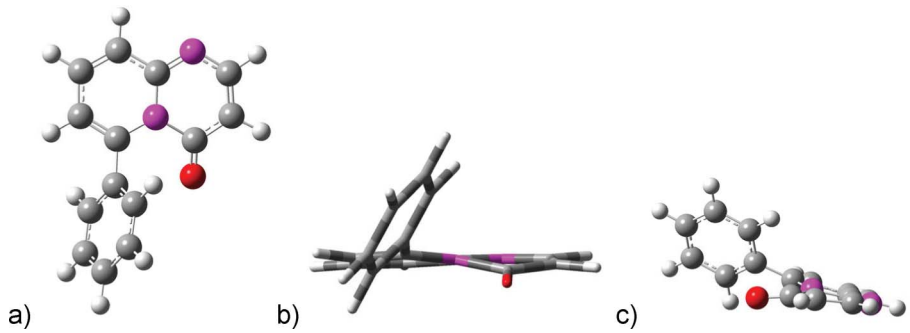


Fig. 1 Calculated ground-state geometry of **48**. a) The ring atoms of the bicycles are in the plane of the drawing. b) The N5–C9*a* bond is perpendicular to the plane of the drawing. c) The line determined by C4 and C6 is almost perpendicular to the plane of the drawing.

electronic properties of the substituent at position 6 of the pyridine moiety and the applied reaction period.[31] The driving force of the formation of 1,4-dihydro-1,8-naphthyridin-4-ones is the release of the strain in 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, accumulated in the ground state between the C4═O group and the C6 substituent. To minimize the steric strain in the ground state of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, the C6 substituent and the C4═O group move in opposite directions out of the plane of the bicycle.

We carried out DFT calculations to determine the potential ground-state structure of 6-phenyl derivative **48**. The result of the calculation is depicted in Fig. 1, and the characteristic geometric data are collected in Table 4, together with the corresponding data on the unsubstituted and 6-methyl derivatives, **45a** and **45b**, respectively.

For characterization of the steric demand of a substituent, we used Charton's υ values,[32] derived from the van der Waals radii (Table 5). The phenyl group could be characterized by minimum and maximum values. The actual size[33] depends on the interplanar angle (between the plane of the phenyl group and the best plane of the bicycle), which is ~55° according to the calculations. In accordance with the Charton's υ values, the calculations also indicated that the steric demand of the 6-phenyl group was somewhat greater than that of the 6-methyl group, as the calculated O═C4···C6–R torsion angle (28.2°) is almost twice that in **45b** (15.2°) (see rows 2 and 4 in the last column in Table 4).

The above expectation is in accordance with the experimental results. When aminomethylenemalonate **46** was added to boiling diphenyl ether, and the reaction mixture was cooled to room temperature within 2 min, we obtained **48** in 68% yield, accompanied by a 18% yield of 1,4-dihydro-1,8-naphthyridin-4-one **47**. Under similar conditions, isopropylidene (6-methyl-2-pyridyl)aminomethylenemalonate afforded the main product **45b** with only a trace of 7-methyl-1,4-dihydro-1,8-naphthyridin-4-one. It is interesting, that in the thermal cyclization of isopropylidene [2-(4-methoxyphenyl)pyrimidin-2-ylaminomethylenemaloanate (a 6-aza analog of **46**) Lesher *et al.*[34] obtained only the thermodynamically more stable 2-(4-methoxyphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidin-5-one (a 6-aza analog of **47**) in a yield of 75% when they applied a slightly longer reaction time (4 min). They did not attempt to identify the nitrogen bridgehead bicycle, 6-(4-methoxyphenyl)-4*H*-pyrimido[1,6-*a*]pyrimidin-4-one (an 7-aza analog of **48**). When we applied 5 min reaction period (instead of 2 min) to the thermal cyclization of **46** (6-phenylpyridin-2-ylamino)methylenemalonate **47** in boiling diphenyl ether 1,8-naphthyridin-4-one formed in a higher yield (37%).

Table 5 Charton's υ steric parameters of the investigated 6-R substituents[32]

	H	Me	Ph
Charton's υ value	0	0.52	0.57 (min); 2.15 (max); 1.66

By crystallization from EtOH, we obtained a single-crystal of **48**, which was suitable for single-crystal X-ray analysis (Fig. 2). The agreement between the theoretical and experimental data on **48** was fair (see rows 4 and 5 in Table 4), considering that the theoretical calculations gave data relating to a vacuum, while in the solid state the crystal packaging exerts some influence on the geometrical parameters. The measured O═C4···C6–R torsion angle (see Table 4) and the interplanar angle were 31(2)° and 54°, respectively. Intermolecular hydrogen-bonding and π–π stacking stabilize the crystal structure of **48**. Non-classical weak hydrogen-bonding [C4═O···H–C = 255.0 pm, and <(O···H–C) = 169°] occurs between the oxygen of the C4═O group and one of the

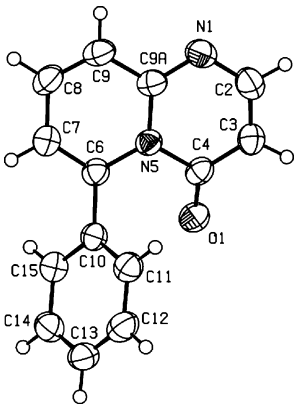


Fig. 2 Molecular diagram of **48** with the numbering atoms (ADP ellipsoids represent 50% probabilities).

meta-hydrogen atoms on the phenyl ring of another molecule, and the perpendicular distance between the pyrimidone rings of the two bicycles is 352.8(6) pm (see the Electronic supplementary information†).

In conclusion, the palladium-catalyzed Suzuki–Miyaura coupling of monohalogen derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with various boronic acids proceeded smoothly under mild reaction conditions, providing different (het)aryl and pentenyl derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in good to excellent yields. The reaction sequence for the halogen atoms at different positions of this bicycle was 8 ≥ 2 > 9 > 7> 3, which was predicted almost correctly by the rule of Handy and Zhang. In accordance with the literature data, the sequence of reactivity I > Br > Cl was observed at each position. Enhanced hydrodehalogenation is characteristic for 3-halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, and especially the 3-iodo compound. The thermal cyclization of isopropylidene [(6-phenylpyridin-2-yl)aminomethylene]malonate afforded 6-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one together with the thermodynamically more stable 7-phenyl-1,4-dihydro-4*H*-1,8-naphthyridin-4-one.

Experimental

General information

Boronic acids, benzylboronic acid pinacol ester, $PdCl_2$ and PPh_3 were purchased from Aldrich and were used without further purification. Melting points were recorded on a Büchi 535 apparatus in open capillary tubes and are uncorrected. UV spectra were recorded on an Agilent 8453 UV-Visible spectrometer, and IR spectra with a VERTEX 70 instrument (KBr). The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-200 or 400 spectrometers in DMSO-d_6 with internal standards, and J values are given in Hz. Mass spectra (GC-MS) were performed on a Shimadzu GCMS-QP2010S instrument, high resolution mass spectra with a Waters LCT Premier XE instrument.

Suzuki–Miyaura cross-couplings

General procedure. To a solution of the monohalogenated derivative of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one[17] (0.25 mmol), boronic acid (0.26 mmol) in DME (1.5 mL) and 1 M $NaHCO_3$ solution (0.6 mL, 0.53 mmol) were introduced. The mixture was heated to 80 °C, after which $Pd(PPh_3)_4$ (14 mg, 0.01 mmol) was added. After stirring at 80 °C for 1 h–96 h, the mixture was allowed to cool to RT, and was then poured into water (3 mL), and extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel [Kieselgel 60 (Reanal); eluent *n*-hexane : ethyl acetate = 1 : 1, except for compounds **34**, **35**, **42**, where 95 : 5 mixture of ethyl acetate and methanol was used as eluent].

2-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7). Yellow crystals (51 mg, 91%; mp. 147–148 °C, *Lit*., mp 149.5–150 °C,[35] 147.5–148 °C,[36] 144–145 °C,[37] 148–149 °C[38]). UV λ_{max}(EtOH)/nm 204 (ε/dm^3 mol^{-1} cm^{-1} 26 800), 274 (27 500), 350 (8800) IR (KBr): ν_{max}/cm^{-1} 3134 (C–H_{Ar}), 1710, 1671 (C═O), 1631 (C═N), 1556, 1531, 1498 (C═C_{Ar}), 756, 673 [γ(═CH)$_{Ar}$]. ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 8.95 (dd, $^3J_{6,7}$ = 6.9 Hz, $^4J_{6,8}$ = 1.6 Hz, 1H, 6-H), 8.21–8.16 (m, 2H, 2′-H and 6′-H), 7.96 (ddd, $^3J_{7,8}$ = 6.9 Hz, $^3J_{8,9}$ = 8.6 Hz, $^4J_{6,8}$ = 1.6 Hz, 1H, 8-H), 7.74 (dd, $^3J_{8,9}$ = 8.6 Hz, $^4J_{7,9}$ = 1.2 Hz, 1H, 9-H), 7.53–7.50 (m, 3H, 4′-H, 3′-H and 5′-H), 7.33 (dt, $^3J_{6,7}$ = $^3J_{7,8}$ = 6.9 Hz, $^4J_{7,9}$ = 1.2 Hz, 1H, 7-H), 6.98 (s, 1H, 3-H). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 160.8 (C-2), 158.1 (C-4), 151.1 (C-9*a*), 138.0 (C-8), 137.1 (C-1′), 131.1 (C-4′), 129.1 (C-3′ and C-5′), 127.64 (C-2′ and C-6′), 127.35 (C-6), 126.6 (C-9), 116.5 (C-7), 99.0 (C-3). MS(EI+): m/z = 222 [M$^+$], 194, 78, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0877.

3-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8). Yellow crystals (55 mg, 98% (Cl); 39 mg, 70% (Br); 41 mg, 73% (I); mp 167–168 °C, *Lit*., mp 167–168 °C,[23a] 166–167 °C[39]). UV λ_{max}(EtOH)/nm 202 (ε/dm^3 mol^{-1} cm^{-1} 29 900), 240 (15 100), 362 (17 100). IR (KBr): ν_{max}/cm^{-1} = 3136, 3093 (C–H_{Ar}), 1670 (C═O), 1626 (C═N), 1574, 1562, 1524, 1494 (C═C_{Ar}), 773, 718 (γ(═CH)$_{Ar}$). ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 9.11 (dd, $^3J_{6,7}$ = 7.1 Hz, $^4J_{6,8}$ = 1.6 Hz, 1H, 6-H), 8.61 (s, 1H, 2-H), 7.98 (ddd, $^3J_{8,9}$ = 9.0 Hz, $^3J_{7,8}$ = 7.8 Hz, $^4J_{6,8}$ = 1.6 Hz, 1H, 8-H), 7.83 (dd, $^3J_{2',3'}$ = 7.2 Hz, $^4J_{2',4'}$ = 1.5 Hz, 2H, 2′-H and 6′-H), 7.74 (d, $^3J_{8,9}$ = 9.0 Hz, 1H, 9-H), 7.46–7.34 (overlapping m, 4H, 7-H, 3′-H, 4′-H and 5′-H). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 156.3 (C-4), 153.0 (C-2), 150.7 (C-9*a*), 137.4 (C-8), 134.8 (C-1′), 128.6 (C-3′, C-5′, C-2′ and C-6′), 127.75 and 127.66 (C-6 and C-4′), 126.4 (C-9), 117.2 (C-7), 115.4 (C-3). MS(EI+): m/z = 222 [M$^+$], 194, 78, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0875.

7-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9). Yellow crystals [51 mg, 92% (Cl); 50 mg, 91% (Br); 48 mg, 87% (I); mp 138–139 °C]. UV λ_{max}(EtOH)/nm 204 (ε/dm^3 mol^{-1} cm^{-1} 25 600), 246 (20 700), 351 (12 900). IR (KBr): ν_{max}/cm^{-1} 3072 (C–H_{Ar}), 1695 (C═O), 1628 (C═N), 1557, 1524, 1497 (C═C_{Ar}), 770, 695 (γ(═CH)$_{Ar}$). ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 9.10 (s, 1H, 6-H), 8.33–8.28 (overlapping m, 2H, 2-H and 8-H), 7.79–7.73 (overlapping m, 3H, 2′-H, 6′-H and 4′-H), 7.57–7.39 (overlapping m, 3H, 3′-H, 5′-H and 9-H), 6.41 (d, $^3J_{2,3}$ = 6.4 Hz, 1H, 3-H). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 157.3 (C-4), 155.0 (C-2), 150.9 (C-9*a*), 136.9 (C-8), 135.3 (C-1′), 129.8 (C-3′ and C-5′), 129.2 (C-9), 129.0 (C-7), 127.2 (C-2′ and C-6′), 126.8 (C-4′), 123.8 (C-6), 104.3 (C-3). MS(EI+): m/z = 222 [M$^+$], 194, 154, 127, 77. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0876.

8-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (10). Yellow crystals [54 mg, 97% (Cl); 51 mg, 92% (Br); mp 184–185 °C]. UV λ_{max}(EtOH)/nm 205 (ε/dm^3 mol^{-1} cm^{-1} 29 300), 272 (18 700), 357 (14 700). IR (KBr): ν_{max}/cm^{-1} = 3100 (C–H$_{Ar}$), 1673 (C═O), 1632 (C═N), 1570, 1512, 1474 (C═C$_{Ar}$), 770, 759 (γ(═CH)$_{Ar}$).^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 9.01 (d, $^3J_{6,7}$ = 7.4 Hz, 1H, 6-H), 8.32 (d, $^3J_{2,3}$ = 6.3 Hz, 1H, 2-H), 8.00–7.94 (m, 3H, 9-H, 2′-H and 6′-H), 7.78 (dd, $^3J_{6,7}$ = 7.4 Hz, $^4J_{7,9}$ = 2.1 Hz, 1H, 7-H), 7.63–7.50 (m, 3H, 3′-H, 5′-H and 4′-H), 6.37 (d, $^3J_{2,3}$ = 6.3 Hz, 1H, 3-H). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 157.1 (C-4), 155.5 (C-2), 152.1 (C-8), 147.8 (C-9*a*), 135.6 (C-1′), 130.7 (C-4′), 129.7 (C-3′ and C-5′), 127.8 (C-6), 127.6 (C-2′ and C-6′), 121.9 (C-9), 115.3 (C-7), 103.8 (C-3). MS(EI+): m/z = 222 [M$^+$], 194, 154, 140, 127, 97, 77, 63, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0877.

9-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (11). Yellow crystals [46 mg, 82% (Cl); 53 mg, 95% (Br); 49 mg, 89% (I); mp 176 °C]. UV λ_{max} (EtOH)/nm 203 (ε/dm^3 mol^{-1} cm^{-1} 28 200), 236 (10 000), 341 (13 200). IR (KBr): ν_{max}/cm^{-1} = 3097, 3048 (C–H$_{Ar}$), 1674 (C═O), 1623 (C═N), 1573, 1528, 1496 (C═C$_{Ar}$), 766, 702 [γ(═CH)$_{Ar}$]. ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 9.03 (dd, $^3J_{6,7}$ = 7.2 Hz, $^4J_{6,8}$ = 1.4 Hz, 1H, 6-H), 8.28 (d, $^3J_{2,3}$ = 6.3 Hz, 1H, 2-H), 7.95 (dd, $^3J_{7,8}$ = 6.8 Hz, $^4J_{6,8}$ = 1.4 Hz, 1H, 8-H), 7.65–7.58 (m, 2H, 2′-H and 6′-H), 7.51–7.38 (overlapping m, 4H, 7-H, 3′-H, 4′-H and 5′-H), 6.43 (d, $^3J_{2,3}$ = 6.3 Hz, 1H, 3-H). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 157.5 (C-4), 154.5 (C-2), 150.5 (C-9*a*), 137.3 (C-9 or C-1′), 137.1 (C-8), 136.8 (C-1′ or C-9), 130.4 (C-2′ and C-6′), 128.4 (C-4′), 128.2 (C-3′ and C-5′), 126.9 (C-6), 116.4 (C-7), 104.0 (C-3). MS(EI+): m/z = 221[M − H$^+$], 193, 154, 140, 127, 97, 77, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0876.

Isopropylidene (6-phenylpyridin-2-ylamino)methylenemalonate (46). A 1 : 2 mixture of Meldrum's acid (1.76 g, 12 mmol) and HC(OMe)$_3$ (3 mL, 25 mmol) was heated under reflux for 4 h, and the reaction mixture was then evaporated to dryness. The residue was dissolved in EtOH (20 mL), 2-amino-6-phenylpyridine (1.70 g, 10 mmol) was added, and the reaction mixture was stirred at ambient temperature overnight. The resulting precipitate was filtered off, washed with EtOH, and recrystallized from EtOH. Yellow crystals (2.19 g, 68%; mp 208 °C, decomp.). ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ 11.43 (br, 1H, NH), 9.39 (s, 1H, ═CH), 8.10 (d, $^3J_{2',3'}$ = 8.0 Hz, 2H, 2′-H and 6′-H), 7.97 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 7.6 Hz, 1H, 4-H), 7.85 (d, $^3J_{4,5}$ = 7.6 Hz, 1H, 5-H), 7.61–7.44 (overlapping m, 4H, 3-H, 4′-H, 3′-H and 5′-H), 1.70 (s, 6H, CH$_3$). ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C): δ 163.7 (br, C-2 and C-4), 155.5 (C-6′), 150.9 (CH), 149.8 (C-2′), 140.9 (C-4′), 138.0 (C-1″), 130.1 (C-4″), 129.4 (C-3″ and C-5″), 127.0 (C-2″ and C-6″), 118.3 (C-5′), 113.2 (C-3′), 104.8 (C-6), 88.6 (C-3), 27.0 (CH$_3$). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.78; H, 4.93; N, 8.65%.

7-Phenyl-1,4-dihydro-1,8-naphthyridin-4-one and (47) 6-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (48). Isopropylidene (6-phenylpyridin-2-ylamino)methylenemalonate (**46**) (2.00 g, 6.2 mmol) was added to Ph_2O (20 g), preheated to 260 °C. The reaction mixture was heated at 260 °C for 2 min, and then quickly cooled to room temperature, and the precipitate was filtered off and washed with n-hexane to give 7-phenyl-1,4-dihydro-1,8-naphthyridin-4-one (**47**) (246 mg 18%, mp 286–287 °C) ^{1}H NMR (400 MHz, DMSO-d_6, 27 °C): δ 12.17 (d, $^3J_{1,2}$ = 4.8 Hz, 1H, NH), 8.51 (d, $^3J_{5,6}$ = 8.3 Hz, 1H, 5-H), 8.19 (dd, $^3J_{2',3'}$ = 7.8 Hz, $^4J_{2',4'}$ = 1.4 Hz, 2H, 2′-H and 6′-H), 7.97 (d, $^3J_{5,6}$ = 8.3 Hz, 1H, 6-H), 7.94 (dd, $^3J_{2,3}$ = 6.9 Hz, $^3J_{1,2}$ = 4.8 Hz, 1H, 2-H), 7.58–7.53 (m, 3H, 3′-H, 4′-H and 5′-H), 6.11 (d, $^3J_{2,3}$ = 6.9 Hz, 1H, 3-H). ^{13}C NMR (100 MHz, DMSO-d_6, 27 °C): δ 177.5 (C-4), 159.1 (C-7), 150.6 (C-8*a*), 140.7 (C-2), 137.6 (C-1′), 136.0 (C-5), 130.5 (C-4′), 129.1 (C-3′ and C-5′), 127.5 (C-2′ and C-6′), 119.3 (C-4*a*), 116.8 (C-6), 110.1 (C-3). MS(EI+): m/z = 222 [M$^+$], 207, 194, 166, 140, 97, 84, 63, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0870.

The mother liquor was diluted with n-hexane (40 mL) and extracted with 2 M HCl. The pH of the separated aqueous phase was adjusted to 8 with aqueous NaOH, and the precipitate was filtered off, washed with water, and recrystallized from EtOH to give 6-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**48**) as yellow crystals (610 mg, 44%; mp 173 °C). UV λ_{max}(EtOH)/nm 203 (ε/dm^3 mol^{-1} cm^{-1} 30 200), 250 (7800), 293 (8500) 359 (8900). IR (KBr): ν_{max}/cm^{-1} = 3058, 3046 (C–H$_{Ar}$), 1686 (C═O), 1629 (C═N), 1569, 1536, 1494 (C═C$_{Ar}$), 763, 700 (γ(═CH)$_{Ar}$). ^{1}H NMR (400 MHz, DMSO-d_6, 27 °C): δ 8.21 (d, $^3J_{2,3}$ = 6.2 Hz, 1H, 2-H), 7.83 (dd, $^3J_{8,9}$ = 8.9 Hz, $^3J_{7,8}$ = 6.9 Hz, 1H, 8-H), 7.60 (dd, $^3J_{8,9}$ = 8.9 Hz, $^4J_{7,9}$ = 1.4 Hz, 1H, 9-H), 7.38–7.34 (m, 3H, 2′-H, 6′-H and 4′-H), 7.32–7.29 (m, 2H, 3′-H and 5′-H), 7.07 (dd, $^3J_{7,8}$ = 6.9 Hz, $^4J_{7,9}$ = 1.4 Hz, 1H, 7-H), 6.24 (d, $^3J_{2,3}$ = 6.2 Hz, 1H, 3-H). ^{13}C NMR (100 MHz, DMSO-d_6, 27 °C): δ 159.1 (C-4), 153.45 (C-9*a*), 153.33 (C-2), 143.1 (C-6), 137.7 (C-1′), 135.6 (C-8), 127.85 (C-4′), 127.45 (C-2′ and C-6′), 126.7 (C-3′ and C-5′), 126.0 (C-9), 120.8 (C-7), 106.2 (C-3). MS(EI+): m/z = 222 [M$^+$], 194, 167, 154, 127, 78, 51. HRMS(ES+) Calculated for $C_{14}H_{11}N_2O$ 223.0871 (MH$^+$), found 223.0868.

Acknowledgements

A. M. acknowledges support through Sanofi-aventis and Pro-Pogressio Foundation fellowships. This article is part 96 of Nitrogen Bridgehead Compounds. For part 95, see ref. 31a.

References

1 (*a*) R. W. DeSimone, K. S. Currie, J. W. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Through. Screen.*, 2004, **7**, 473–493; (*b*) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235–2246.
2 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 1997, **23**, 3–25.
3 (*a*) I. Hermecz and L. Vasvári-Debreczy, *Comprehensive Heterocyclic Chemistry III*, 2007, **12**, 77–217, Vol. Ed. K. Jones, Execut. Ed.: A. R. Katritzky; (*b*) I. Hermecz, L. Vasvári-Debreczy and P. Mátyus, *Comprehensive Heterocyclic Chemistry II*, 1996, **8**, 563–595. Vol Ed. G. Jones, ed.: A. R. Katritzky, C. W. Rees, E. F. V. Scriveb; (*c*) I. Hermecz and Z. Mészáros, *Med. Res. Rev.*, 1988, **8**, 203–230.
4 (*a*) Pharm Exec Staff, *Pharmaceut. Exec.*, 2007, (5), 98–110; (*b*) C. Fenton and L. J. Scott, *CNS Drugs*, 2005, **19**, 429–444; (*c*) T. S. Harrison and K. L. Goa, *CNS Drugs*, 2004, **18**, 113–132.
5 (*a*) L. P. H. Yang and G. L. Plosker, *CNS Drugs*, 2007, **21**, 417–425; (*b*) R. T. Owen, *Drugs Today*, 2007, **43**, 249–258.
6 (*a*) S. M. Hoy, L. J. Scott and G. M. Keating, *CNS Drugs*, 2010, **24**, 227–244; (*b*) R. T. Owen, *Drugs Today*, 2010, **46**, 463–471.
7 (*a*) I. Hermecz, *Adv. Heterocycl. Chem.*, 2003, **85**, 173–285; (*b*) I. Hermecz, *Adv. Heterocycl. Chem.*, 1995, **63**, 103–275; (*c*) I. Hermecz and Z. Mészáros, *Adv. Heterocycl. Chem.*, 1983, **33**, 241–330.

8 A. Lochead, M. Saady and P. Yaiche, *Eur. Pat. Appl.*, 2 138 493, 2009.
9 (*a*) X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 9047–9050; (*b*) M. Seki, *Synthesis*, 2006, 2975–2992; (*c*) *Metal Catalyzed Cross-Coupling Reactions* 2nd edn (ed.: A. de Meijere, F. Diederich) Wiley-VHC, Weinheim, 2004; (*d*) Cross-Coupling Reactions. A practical Guide (Ed.: N. Miyaura) *Topics Curr. Chem.*, vol 219, Springer Verlag, Berlin, 2002.
10 (*a*) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2117–2250; (*b*) V. F. Slagt, A. H. M. de Vries, J. G. de Vries and R. M. Kellogg, *Org. Process Res. Dev.*, 2010, **14**, 30–47; (*c*) C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043; (*d*) H. Doucet and J.-C. Hierso, *Curr. Opin. Drug. Disc. Dev.*, 2007, **10**, 672–690; (*e*) H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven and A. Schnyder, *Adv. Synth. Catal.*, 2004, **346**, 1583–1598.
11 S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245–2267.
12 (*a*) A. Suzuki, *Heterocycles*, 2010, **80**, 15–43; (*b*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633–9695; (*c*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147–168; (*d*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*e*) A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178–184.
13 Palladium mediated cross-coupling reaction in position 2 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones: (*a*) K. Yoshida, K. Nakayama, N. Kuru, S. Kobayashi, M. Ohtsuka, M. Takemura, K. Hoshino, H. Kanda, J. Z. Zhang, V. J. Lee and W. J. Watkins, *Bioorg. Med. Chem.*, 2006, **14**, 1993–2004; (*b*) K. Yoshida, K. Nakayama, Y. Yokomizo, M. Ohtsuka, M. Takemura, K. Hoshino, H. Kanda, K. Namba, H. Nitanai, J. Z. Zhang, V. J. Lee and W. J. Watkins, *Bioorg. Med. Chem.*, 2006, **14**, 8506–8518.
14 Palladium mediated cross-coupling reaction in position 3 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones: (*a*) D. Bussiere, M. Knapp, V. P. Le and E. Martin, *US Pat.* 7 662 581, 2010; (*b*) V. S. P Lingam, A. Thomas, D. A. More, J. Y. Khatik, J. N. Khairatkar, and V. G. Kattige, *PTO Int Appl. WO* 2009/109987, 2009; (*c*) A.-R. Li, M. G. Johnson, J. Liu, X. Chen, X. Du, J. T. Mihalic, J. Deignan, D. J. Gustin, J. Duquette, Z. Fu, L. Zhu, A. P. Marcus, P. Bergeron, L. R. McGee, J. Danao, B. Lemon, T. Carabeo, T. Sullivan, J. Ma, L. Tang, G. Tonn, T. L. Collins and J. C. Medina, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 688–693; (*d*) S. Liu, J. Fu, R. Kamboj, Q. Jia, M. Wood, S. Chowdhury, and J. Sun, *PTO Int Appl. WO* 2008/097991, 2008; (*e*) P. Bergeron, X. Chen, X. Du, J. Deignan, J. A. Duquette, D. Gustin, J. Medina, J. T. Mihalic, and G. R. Tonn, *PTO Int Appl. WO* 2007/002701, 2007; (*f*) W. Wang, R. N. Constantine, L. M. Lagniton, S. Pecchi, M. T. Burger, and M. C. Desai, *PTO Int Appl. WO* 2004/11335, 2004.
15 Palladium mediated cross-coupling reaction in position 7 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones: M. J. O'Mahony, P. J. West, S. D. Lindell and J. A. Macritchie, *Brit. Pat.*, 2 307 177, 1997.
16 Palladium mediated cross-coupling reaction in position 9 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones: (*a*) A. Palani, A. U. Rao, X. Chen, N. Shao, Y. R. Huang, and R. G. Aslanian, *PTO Int Appl. WO* 2010/071819, 2010; (*b*) O. R. Barbeau, C. Cano-Soumillac, R. J. Griffin, I. R. Hardcastle, G. C. M. Smith, C. Richardson, W. Clegg, R. W. Harrington and B. T. Golding, *Org. Biomol. Chem.*, 2007, **5**, 2670–2677; (*c*) G. C. M. Smith, N. M. B. Martin, M. G. Hummersone, K. A. Menear, X.-L. F. Cockcroft, M. Frigerio, R. J. Griffin, B. T. Golding, I. R. Hardcastle, D. R. Newell, H. A. Calvert, N. J. Curtin, K. Saravanan, and M. Desage-El Murr, *PTO Int Appl. WO* 2006/109081, 2006; (*d*) Z. A. Knight, G. G. Chiang, P. J. Alaimo, D. M. Kenski, C. B. Ho, K. Coan, R. T. Abraham and K. M. Shokat, *Bioorg. Med. Chem.*, 2004, **12**, 4749–4759.
17 A. Molnár, F. Faigl, B. Podányi, Z. Finta, L. Balázs and I. Hermecz, *Heterocycles*, 2009, **78**, 2477–2488 and references cited therein.
18 (*a*) Y. Garcia, F. Schoenebeck, C. Y. Legault, C. A. Merlic and K. N. Houk, *J. Am. Chem. Soc.*, 2009, **131**, 6632–6639; (*b*) C. Y. Legault, Y. Garcia, C. A. Merlic and K. N. Hauk, *J. Am. Chem. Soc.*, 2007, **129**, 12664–12665; (*c*) A. Ariafard and Z. Lin, *Organometallics*, 2006, **25**, 4030–4033.
19 S. T Handy and Y. Zhang, *Chem. Commun.*, 2006, 299–301.
20 I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036–1045.
21 G. J. Karabatsos, G. C. Sonnichsen, N. Hsi and D. J. Fenoglio, *J. Am. Chem. Soc.*, 1967, **89**, 5067–5068.
22 D. R. Coulson, *Inorg. Synth.*, 1990, **28**, 107–109.
23 (*a*) G. Náray-Szabó, I. Hermecz and Z. Mészáros, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1753–1756; (*b*) G. R. Lappin, *J. Am. Chem. Soc.*, 1949, **71**, 3258–3259.
24 (*a*) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020–4028; (*b*) P. Fitton and E. A. Rick, *J. Organomet. Chem.*, 1971, **28**, 287–291.
25 (*a*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176–4211; (*b*) D.-H. Lee, M. Choi, B.-W. Yu, R. Ryoo, A. Taher, S. Hossain and M.-J. Jin, *Adv. Synth. Catal.*, 2009, **351**, 2912–2920.
26 (*a*) C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev.*, 2010, **39**, 694–711; (*b*) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555–1564; (*c*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.
27 E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768–2813.
28 (*a*) Á. Molnár, *Chem. Rev.*, 2011, **111**, 2251–2320; (*b*) J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527–2572; (*c*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, 2419–2440; (*d*) W. A. Herrmann, K. Öfele, D. von Preysing and S. K. Schneider, *J. Organomet. Chem.*, 2003, **687**, 229–248(b).
29 P. Appukkuttan and E. Van der Eycken, *Eur. J. Org. Chem.*, 2008, 1133–1155.
30 P. L. Ferrarini, C. Mori, C. Manera, F. Mori, V. Calderone and E. Martinotti, *J. Heterocycl. Chem.*, 1999, **36**, 1123–1127.
31 (*a*) A. Molnár, Z. Mucsi, G. Vlád, K. Simon, T. Holczbauer, B. Podányi, F. Faigl and I. Hermecz, *J. Org. Chem.*, 2011, **76**, 696–699; (*b*) I. Hermecz, L. Vasvári-Debreczy and K. Simon, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1287–1289; (*c*) I. Hermecz, Z. Mészáros, K. Simon, L. Szabó and Z. Pál, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1795–1798; (*d*) I. Hermecz, Z. Mészáros, Z. L. Vasvári-Debreczy, Á. Horváth, G. Horváth and M. Pongor-Csákvári, *J. Chem. Soc., Perkin Trans. 1*, 1977, 789–795; (*e*) Mészáros and I. Hermecz, *Tetrahedron Lett.*, 1975, **16**, 1019–1020.
32 M. Charlton, *J. Am. Chem. Soc.*, 1975, **97**, 1552–1556.
33 (*a*) M. Charton, *Kémiai Közlemények*, 1991, **73**, 13–27; (*b*) M. Charton, *J. Org. Chem.*, 1983, **48**, 1011–1015.
34 B. Singh, S. C. Laskowski and G. Y. Lesher, *Synlett*, 1990, 549–550.
35 I. T. Barnish and C. R. Hauser, *J. Org. Chem.*, 1968, **33**, 2116–2118.
36 A. Mendel, *J. Heterocycl. Chem.*, 1972, **9**, 935–936.
37 H. G. Bonacorso, F. J. Righi, I. R. Rodrigues, C. A. Cechinel, M. B. Costa, A. D. Wastowski, M. A. P. Martins and N. Zanatta, *J. Heterocycl. Chem.*, 2006, **43**, 229–233.
38 C. La Motta, S. Sartini, L. Mugnaini, F. Simorini, S. Taliani, S. Salerno, A. M. Marini, F. Da Settimo, A. Lavecchia, E. Novellino, M. Cantore, P. Failli and M. Ciuffi, *J. Med. Chem.*, 2007, **50**, 4917–4927.
39 A. Halleux and H. G. Viehe, *J. Chem. Soc. C*, 1970, 881–887.