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SYNTHESIS OF HALOGENATED 4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES[1]

Annamária Molnár,[a,b] Ferenc Faigl,[b,c] Benjamin Podányi,[a] Zoltán Finta,[a] László Balázs,[a] and István Hermecz[a,b*]

[a]Chinoin Ltd, Tó utca 1-5, H-1045 Budapest, Hungary; [b]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8, H-1111 Budapest, Hungary; [c]Research Group for Organic Chemical Technology, Hungarian Academy of Sciences, Budafoki út 8, H-1111 Budapest, Hungary

Abstract – Halogenated 4*H*-pyrido[1,2-*a*]pyrimidin-4-one were synthesized by thermal cyclization and decarboxylation of isopropylidene (2-pyridylamino)methylenemalonates, prepared from 2-aminopyridines and isopropylidene methoxymethylenemalonate formed *in situ*. Instead of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, the 6-chloro and 6-bromo derivatives afforded mixtures of 7-halo-1,4-dihydro-1,8-naphthyridin-4-ones and 1-(6-halo-2-pyridyl)-3-[(6-halo-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridine-2,4-diones. The latters formed from *N*-(2-pyridyl)iminoketenes, the common intermediates of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and 1,8-naphthyridin-4-ones, via a "head-to-tail" [4+2] cycloaddition. 3-Halo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were obtained from 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with *N*-halosuccinimides. The structures of the new compounds were characterized by means of ^{1}H NMR and ^{13}C NMR examinations.

INTODUCTION

The pyrido[1,2-*a*]pyrimidine skeleton is a privileged scaffold for facile access to "drug-like" small molecules,[2] which fulfill the requirements of the rule-of-five.[3] In particular, 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have attracted the attention of pharmaceutical community, as they display diverse biological activities (Figure 1). The best-known 4*H*-pyrido[1,2-*a*]pyrimidin-4-one is the atypical neuroleptic risperidone **1**, which was one of the drugs most widely prescribed worldwide in 2007.[4] Its active metabolite, the antipsychotic paliperidone **2,** was registered by the FDA in 2007 for the

treatment of bipolar disorders.[5] The other outstanding members include the anti-allergic pemirolast **3**,[6] the non-narcotic analgesic rimazolium **4**,[7] an anti-ulcer agent **5**,[8] the tranquillizer pirenperone **6**,[9] the anti-allergic ramastine **7**,[10] the antihypertensive seganserin **8**[11] and the antidepressant lusaperidone **9**.[12]

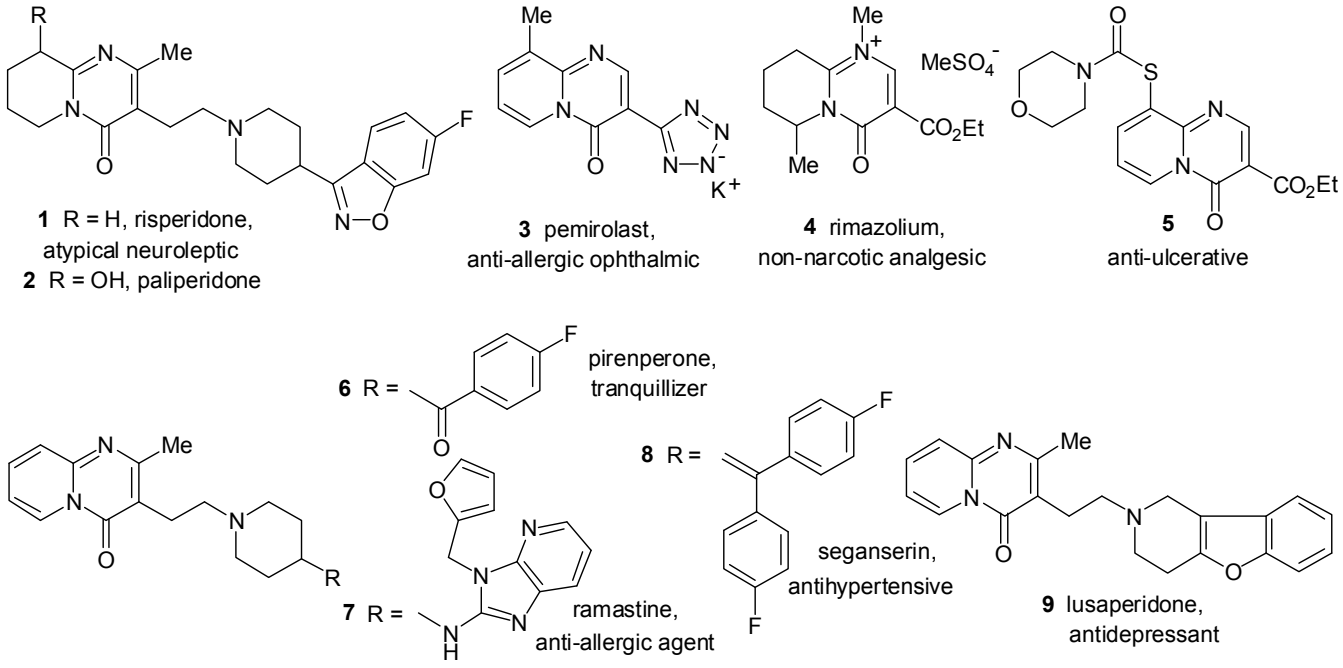


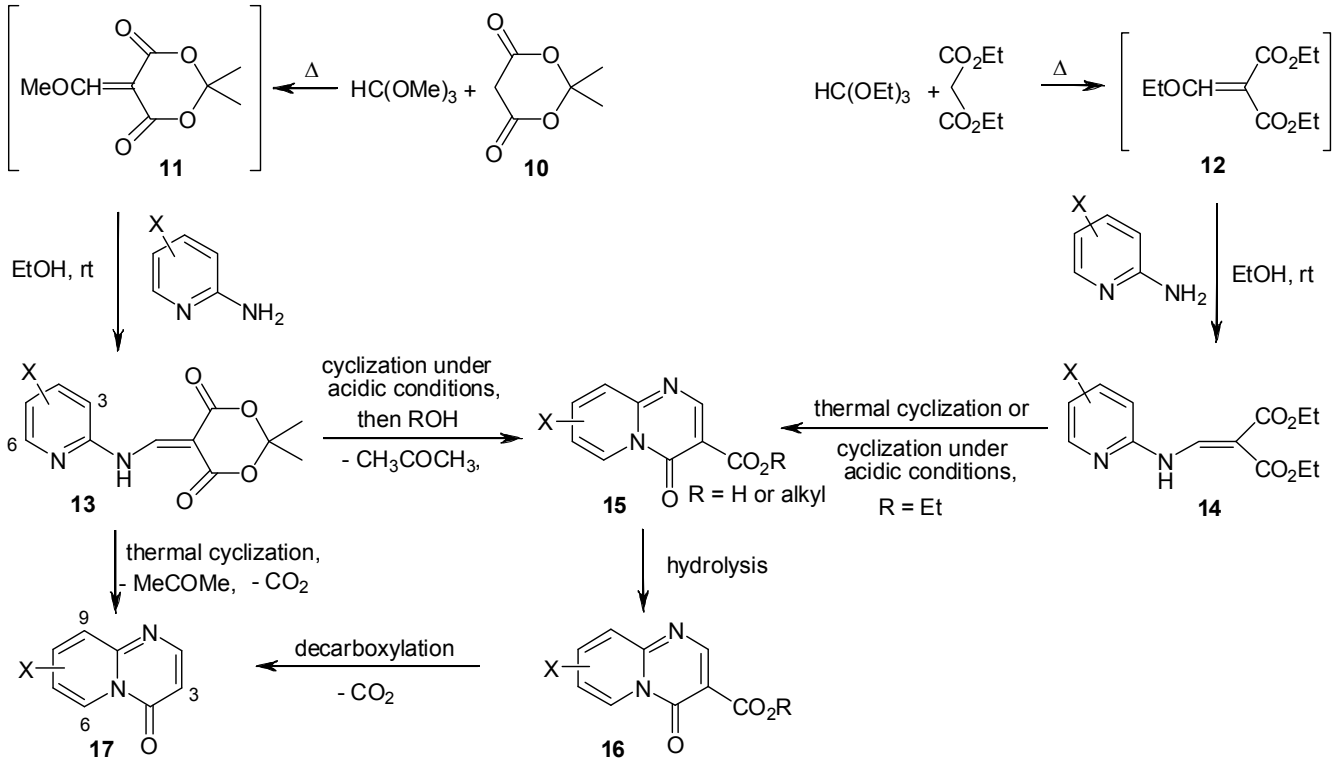
Figure 1. Some biologically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

Transition metal-catalyzed carbon-carbon bond formation is a fundamental reaction for the functionalization of aromatic and heteroaromatic ring systems.[13] To date, no systematic investigation has been reported on 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. Only a few published examples of transition metal-catalyzed carbon-carbon bond formation are to be found for 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[14] In the present paper, we report on the synthesis of different halogen derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, which are very convenient substrates for cross-couplings (e.g. the Suzuki-Miyaura, Heck, Sonogashira, and Buchwald-Hartwig reactions).

RESULTS AND DISCUSSION

For the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17,** Meldrum's acid[15] **10** was selected as starting material instead of dimethyl malonate, because **10** is a stronger CH acid (pK_a = 7.32 ± 0.01 in DMSO[16]) and therefore more reactive than dimethyl malonate (pK_a = 15.87 ± 0.03 in DMSO[16]). Another advantage is that **17** can be obtained from aminomethylenemalonates (**14**) in three reaction steps: cyclization, ester hydrolysis and then decarboxylation,[17] whereas aminomethylenemalonates (**13**) give 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**17**) directly in a one-pot reaction under thermal conditions[18] where decarboxylation and cyclization occur during heating, at around 240-260 °C. The alternative reaction

sequences are depicted in Scheme 1. Carboxylic acid derivatives of nitrogen bridgehead ring systems (e.g. **15**, R = H) could be obtained from isopropylidene (2-hetarylamino)methylenemalonates even under acidic conditions (e.g. in a mixture of $POCl_3$ and PPA at 135-140 °C,[19a] and in PPA[19b]).



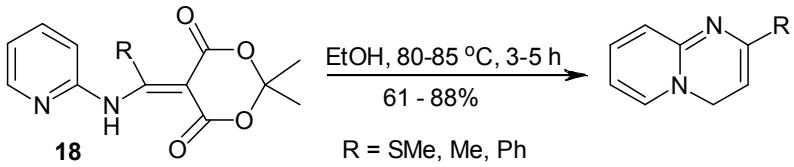
Scheme 1. Alternative synthetic routes for 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17**

The reaction between Meldrum's acid **10** and trimethyl orthoformate smoothly yielded isopropylidene methoxymethylenemalonate (**11**). After the reaction mixture had been heated for 4 h on an oil bath and then evaporated to dryness *in vacuo*, the residue was left to react with the appropriate 2-aminopyridine in EtOH at ambient temperature over night. The precipitated aminomethylenemalonate (**13**) was filtered off from the cooled reaction mixture and used directly in the cyclization step without further purification (yields are shown in Table 1).

The addition of (6-unsubstituted-2-pyridyl)aminomethylenemalonates (**13a-k**) to preheated Ph_2O at 260 °C afforded 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**17**) in good yields after dilution of the cold reaction mixture with hexane and extraction with aqueous 2 *N* HCl, followed by adjustment of the pH of the aqueous extract to 8 with 40% NaOH solution (see Table 1). The precipitated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were filtered off and recrystallized from EtOH. Our work-up protocol provided 15-30% better yields for **17f**, **17i** and **17k** than in the earlier methods[20,21] (50%, 62% and 44%, respectively), where Ph_2O was diluted with pentane or hexane and precipitated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were filtered off. In the case of **17k,** no mp was reported previously.[21]

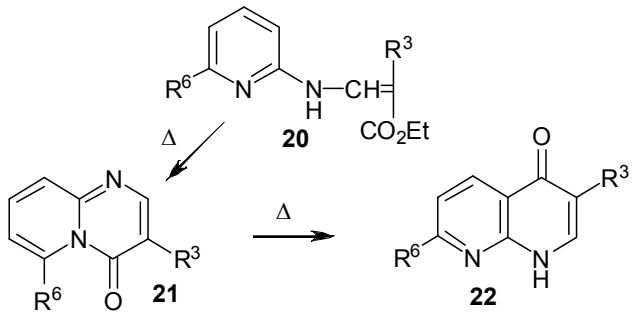
Table 1. Syntheses of aminomethylenemalonates **13a-k** and 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17**

	Compd	X	Yield %	Mp °C	Lit. Mp °C	Compd	X	Yield %	Mp °C	Lit. Mp °C
1	**13a**	H	70	174-175	175.2-176.4[18]	**17a**	H	80	130-131	131-132[22]
2	**13b**	3-F	87	193		**17b**	9-F	65	171	
3	**13c**	5-F	81	200		**17c**	7-F	75	186	
4	**13d**	3-Cl	85	179-180		**17d**	9-Cl	75	148	
5	**13e**	4-Cl	79	222-224		**17e**	8-Cl	59	156-157	
6	**13f**	5-Cl	84	195	193-194[20]	**17f**	7-Cl	81	124	121-123[20]
7	**13g**	3-Br	95	165-166		**17g**	9-Br	84	180-181	
8	**13h**	4-Br	90	228		**17h**	8-Br	63	184-185	
9	**13i**	5-Br	99	188	192-193[20]	**17i**	7-Br	76	125-127	127-130[20]
10	**13j**	3-I	75	180		**17j**	9-I	71	194-196	
11	**13k**	5-I	69	189		**17k**	7-I	66	157-158[21]	



Scheme 2

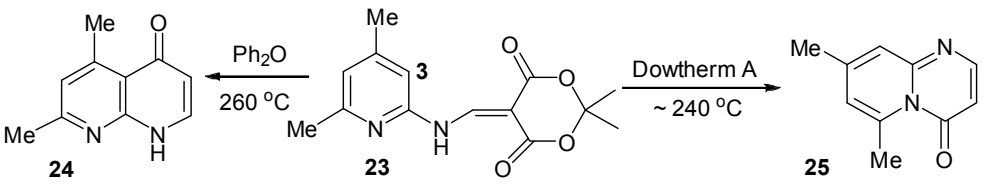
In contrast with what was reported by Ye *et al*.,[23] who have obtained 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**19**) when **18** was heated under reflux in EtOH, we did not observed the formation of any 4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**19**, R = H) from **13h** under similar conditions, even after a longer reaction time (8 h) (Scheme 2).



Scheme 3

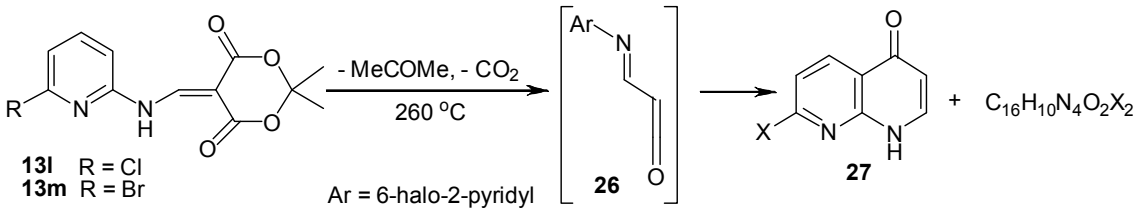
The thermal cyclization of 3-(6-substituted-2-pyridyl)acrylates (**20**) gave 6-substituted-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones (**21**) or 7-substituted-1,4-dihydro-1,8-naphthyridin-4-ones (**22**), or their mixture, depending on the nature of the 2-substituent in the acrylates (R^3) and on the reaction conditions.[24] (Scheme 3) 6-Substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**21**) were transformed into the

thermodynamically more stable 7-substituted-1,4-dihydro-1,8-naphthyridin-4-ones (**22**) by heating at higher temperature or for a longer period.[25]



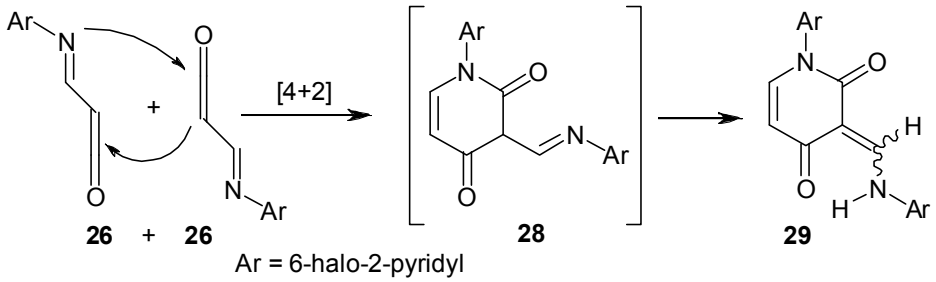
Scheme 4

De Silva et al.[26] obtained 5,7-dimethyl-1,4-dihydro-1,8-naphthyridin-4-one (**24**) by refluxing isopropylidene [*N*-(4,6-dimethyl-2-pyridyl)aminomethylene]malonate (**23**) in Ph_2O, but 4,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**25**) was the product when the ring closure was carried out in Dowtherm A at a lower temperature, ~240 °C.[18] (Scheme 4).



Scheme 5

From the 6-chloro and 6-bromo derivatives of aminomethylenemalonates (**13l, m**) in boiling Ph_2O we expected to obtain 7-halo-1,4-dihydro-1,8-naphthyridin-4-ones (**27**, X = Cl, Br), as the Cl and Br atoms exhibit similar bulkiness[27] to that of the Me group. From the reaction mixtures besides the expected 1,8-naphthyridines **27**, we could isolated by-products, too (Scheme 5). In both cases LC-MS investigations have indicated a dimer formation with brutto formula $C_{16}H_{10}N_4O_2X_2$. (At the thermal cyclization of **13a** dimer formation could not be detetected by LC-MS investigations.) Naphthyridines **27** and dimers **29** could be separated by fractional crystallization from EtOH. Dimers exhibited lower solubility, than naphthyridines. According to our knowledge, these are the first cases when dimeric products were detected and isolated in the case of the thermal cyclization of (6-substituted 2-pyridylamino)methylenemalonates.



Scheme 6

Dimers **29** would be formed in a "head-to-tail" [4+2] cyclodimerization of the iminoketene **26**, which would probably take place in a pseudopericyclic manner, initiated by the attack of an imino lone pair on the carbonyl carbon of a second molecule of iminoketene (Scheme 6). The initial dimer (**28**) thus formed would tautomerizes by 1,3 hydrogen shift to the isolated product **29**. A similar dimer formation was earlier described by Wentrup et al. in the case of 2-pyridylketene.[28] ^{1}H and ^{13}C NMR data are consistent with the dimer structure **29**, and have indicated that the products are present as a 1:2 *E*-*Z* isomeric mixtures in DMSO-d_6 (see Figure 2).

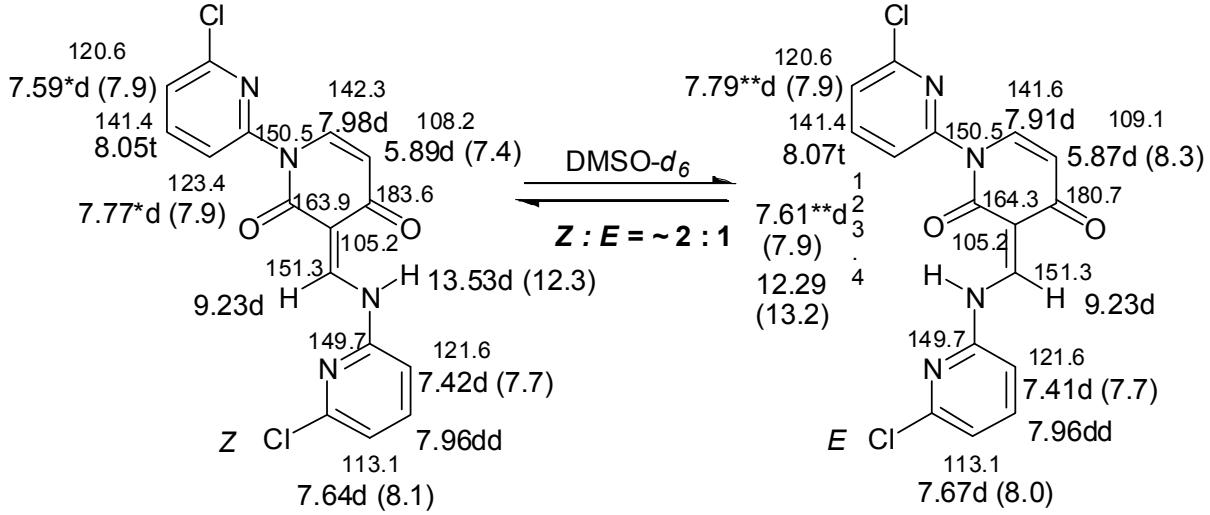
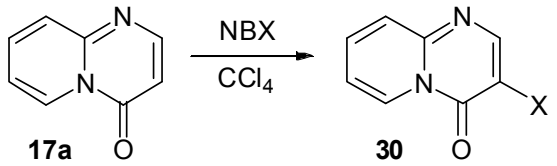


Figure 2. ^{1}H (coupling constant in parenthesis) and identified ^{13}C NMR (bold) data of compound **29a** determined by HSQC, COSY, HBMC experiments in DMSO-d_6. (* and ** indicate that a reverse assignment of these protons is also possible)

Table 2. Syntheses of aminomethylenemalonates **13l,m** and 7-halo-1,4-dihydro-1,8-naphthyridin-4-ones **27**

Entry	Aminomethylenemalonate (**13**)				1,4-dihydro-1,8-naphthyridin-4-ones (**27**)			
	Compound	X	Yield %	Mp ^{o}C	Compound	X	Yield %	Mp ^{o}C
1	**13l**	6-Cl	61	199-200	**27a**	7-Cl	75	> 300
2	**13m**	6-Br	72	205	**27b**	7-Br	69	> 300



Scheme 7

3-Chloro-, 3-bromo- and 3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**30**) were obtained from **17a** in 76-86% yields by reaction with the respective *N*-halosuccinimide in CCl_4 (Scheme 7).

CONCLUSION

In conclusion, a productive "one-pot" synthesis was extended for the preparation of halogenated 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17b-k**) from Meldrum's acid, trimethyl orthoformate and the appropriate 2-aminopyridine via methoxymethylenemalonates (**13**). From the 6-chloro and 6-bromo derivatives **13m, l** a mixture of 7-halo-1,4-dihydro-1,8-naphthyridin-4-ones (**27**) and, in the first case, tetrahydropyridine-2,4-diones **29** were obtained. The latters formed in a "head-to-tail" [4+2] cyclodimerization from the common intermediates **26** of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 1,8-naphthyridin-4-ones. The 3-halo derivatives **30** were obtained from 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**17a**) with *N*-halosuccinimides. The structures of the new compounds were characterized by means of ^{1}H and ^{13}C NMR spectroscopy.

Table 3. ^{1}H NMR data on 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17** and **30** in DMSO-d_6

Compd.	H-2	H-3	H-6	H-7	H-8	H-9	Coupling constants (Hz)
17a	8.31d	6.34d	8.98dd	7.30dd	7.97ddd	7.70d	$J_{2,3}$ = 6.2; $J_{6,7}$ = 7.0; $J_{7,8}$ = 6.9; $J_{8,9}$ = 9.0; $^{4}J_{6,8}$ = 1.6
17b	8.32d	6.48d	8.78d	7.32ddd	7.89ddd	-	$J_{2,3}$ = 6.3; $J_{6,7}$ = 7.1; $J_{7,8}$ = 7.6; $^{2}J_{8,9F}$ = 9.3; $^{4}J_{6,8}$ = 1.2; $^{3}J_{7,9F}$ = 7.6
17c	8.32d	6.42d	8.94dd	-	8.10ddd	7.80dd	$J_{2,3}$ = 6.2; $J_{6,7F}$ = 4.8; $^{4}J_{6,8}$ = 2.8; $J_{7F,8}$ = 7.2; $J_{8,9}$ = 9.8; $^{4}J_{7F,9}$ = 5.4
17d	8.36d	6.48d	8.91dd	7.30t	8.20dd	-	$J_{2,3}$ = 6.4; $J_{6,7}$ = $J_{7,8}$ = 7.3; $^{4}J_{6,8}$ = 1.3
17e	8.26d	6.40d	8.92d	7.40dd	-	7.85d	$J_{2,3}$ = 6.4; $J_{6,7}$ = 7.8; $^{4}J_{7,9}$ = 2.2
17f	8.31d	6.44d	8.95d	-	8.02dd	7.71d	$J_{2,3}$ = 6.2; $J_{8,9}$ = 9.0; $^{4}J_{6,8}$ = 2.4
17g	8.37d	6.46d	8.96dd	7.23t	8.38dd	-	$J_{2,3}$ = 6.4; $J_{6,7}$ = $J_{7,8}$ = 7.2; $^{4}J_{6,8}$ = 1.4
17h	8.27d	6.41d	8.82d	7.50dd	-	8.04d	$J_{2,3}$ = 6.4; $J_{6,7}$ = 7.6; $^{4}J_{7,9}$ = 1.8
17i	8.32d	6.45d	9.02d	-	8.08dd	7.64d	$J_{2,3}$ = 6.2; $J_{8,9}$ = 9.6; $^{4}J_{6,8}$ = 2.0
17j	8.36d	6.34d	8.97d	7.08dd	8.57dd	-	$J_{2,3}$ = 6.4; $J_{6,7}$ = 7.0; $J_{7,8}$ = 7.2; $^{4}J_{6,8}$ = 2.0
17k	8.29d	6.42d	9.08d	-	8.12dd	7.47d	$J_{2,3}$ = 6.2; $J_{8,9}$ = 9.4; $^{4}J_{6,8}$ = 2.2
30a	8.60s	-	9.00dd	7.46ddd	8.02ddd	7.78dd	$J_{6,7}$ = 6.8; $J_{7,8}$ = 7.0; $J_{8,9}$ = 9.0; $^{4}J_{6,8}$ = 1.6; $^{4}J_{7,9}$ = 1.4
30b	8.65s	-	9.00dd	7.45ddd	8.03ddd	7.75dd	$J_{6,7}$ = 7.2; $J_{7,8}$ = 7.0; $J_{8,9}$ = 9.0; $^{4}J_{6,8}$ = 1.4; $^{4}J_{7,9}$ = 1.2
30c	8.72s	-	8.97dd	7.43ddd	8.03ddd	7.72dd	$J_{6,7}$ = 6.7; $J_{7,8}$ = 7.6; $J_{8,9}$ = 8.8; $^{4}J_{6,8}$ = 1.6; $^{4}J_{7,9}$ = 1.4

EXPERIMENTAL

Melting points are uncorrected and yields were not maximized. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker DRX instrument at 400 and 100 MHz, respectively). Coupling constants are reported in Hz and chemical shifts in ppm (δ, ppm) downfield from TMS, which was used as internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), broad (br). LC-MS investigations were carried out by an Alliance 2695 HPLC system (Waters Co.) equipped with a quaternary pump, an auto-sampler, Waters 2996 PDA detector and a Waters ZQ-2000 single quadruple mass spectrometer with ESCi source. Chromatographic separation was carried out at 30 °C on an Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm). The mobile phases consisted of 0.05% CF_3CO_2H in H_2O (A) and 0.03% CF_3CO_2H acid in MeCN (B) using a gradient elution of 5–5% (v/v) B at 0–0.5 min; 5–95% B at 0.5–4.5 min; 95–95% B at 4.5–6.0 min. The flow rate was 0.5 mL/min, and the injection volume was 0.5 μL.

Table 4. ^{13}C NMR data on 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17** and **30** in DMSO-d_6

Compd.	X	C-2	C-3	C-4	C-6	C-7	C-8	C-9	C-9*a*
17a	H	155.1	104.0	157.2	127.4	116.8	137.7	126.4	151.8
17b[a)]	9-F	154.1	105.5	156.7	123.5	114.9	119.6	153.8	144.8
17c[b)]	7-F	154.6	103.7	156.8	124.9	154.3	129.8	127.9	149.9
17d	9-Cl	154.4	105.1	157.1	126.8	115.4	136.7	129.7	148.5
17e	8-Cl	155.6	104.7	156.9	129.0	117.6	142.9	124.6	151.6
17f	7-Cl	154.9	104.7	156.3	127.0	123.7	138.0	127.9	150.3
17g	9-Br	154.7	104.9	157.2	127.5	116.1	140.5	120.4	148.8
17h	8-Br	155.5	104.8	157.0	128.6	120.0	132.2	128.1	151.6
17i	7-Br	154.9	104.8	156.2	127.9	110.9	140.1	127.0	150.3
17j	9-I	154.9	104.3	157.4	128.1	117.1	147.5	98.7	149.5
17k	7-I	154.9	104.7	156.0	131.7	82.3	144.6	127.4	150.2
30a	3-Cl	152.7	110.8	154.3	127.8	117.7	137.8	126.5	150.3
30b	3-Br	155.2	100.6	154.3	127.9	117.8	138.0	126.4	150.8
30c	3-I	160.1	75.6	155.2	128.1	117.9	138.3	126.0	151.2

a) $^{1}J_{C\text{-}9,F}$ = 253,9 Hz; $^{2}J_{C\text{-}9a,F}$ = 20.7 Hz; $^{2}J_{C\text{-}8,F}$ = 17.9 Hz; $^{3}J_{C\text{-}7,F}$ = 7.4 Hz; $^{4}J_{C\text{-}6,F}$ = 4.8 Hz;
b) $^{1}J_{C\text{-}9,F}$ = 242,4 Hz; $^{2}J_{C\text{-}6,F}$ = 41.5 Hz; $^{2}J_{C\text{-}8,F}$ = 25.4 Hz; $^{3}J_{C9,F}$ = 7.9 Hz;

Synthesis of Isopropylidene (2-Pyridylamino)methylenemalonate (13). *General Method*. A 1:2 mixture of Meldrum's acid (17.6 g, 0.12 mol) and trimethyl orthoformate (30 mL, 0.25 mol) was heated under reflux for 4 h, and the reaction mixture was then evaporated to dryness at 100 mbar. The residue **11** was dissolved in EtOH (200 mL) and a 2-aminopyridine (0.1 mol) was added, and the reaction mixture was stirred at ambient temperature overnight. The precipitated **13** was filtered off, washed with

EtOH and used in cyclization reaction without further purification. Yields and mp are listed in Table 1, and the results of the elemental analysis are listed in Table 5.

Table 5. Elemental analyses for new aminomethylenemalonates **13** and 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17**

Compound	*Anal*. Calcd for	Calcd			Found		
		C	H	N	C	H	N
13b	$C_{12}H_{11}FN_2O_4$	54.14	4.16	10.52	53.92	4.15	10.44
13c	$C_{12}H_{11}FN_2O_4$	54.14	4.16	10.52	54.20	4.11	10.57
13d	$C_{12}H_{11}ClN_2O_4$	50.99	3.92	9.91	51.09	3.99	10.07
13e	$C_{12}H_{11}ClN_2O_4$	50.99	3.92	9.91	50.85	3.87	9.95
13g	$C_{12}H_{11}BrN_2O_4$	44.06	3.39	8.56	43.89	3.40	8.52
13h	$C_{12}H_{11}BrN_2O_4$	44.06	3.39	8.56	44.00	3.38	8.68
13j	$C_{12}H_{11}IN_2O_4$	38.52	2.96	7.49	38.69	2.89	7.38
13k	$C_{12}H_{11}IN_2O_4$	38.52	2.96	7.49	38.38	2.99	7.50
13l	$C_{12}H_{11}ClN_2O_4$	50.99	3.92	9.91	51.91	4.14	9.98
13m	$C_{12}H_{11}BrN_2O_4$	44.06	3.39	8.56	43.85	3.51	8.74
17b	$C_8H_5FN_2O$	58.54	3.07	17.07	58.72	2.98	17.21
17c	$C_8H_5FN_2O$	58.54	3.07	17.07	58.52	3.10	17.15
17d	$C_8H_5ClN_2O$	53.21	2.79	15.51	53.34	2.70	15.41
17e	$C_8H_5ClN_2O$	53.21	2.79	15.51	53.30	2.80	15.28
17g	$C_8H_5BrN_2O$	42.70	2.24	12.45	42.91	2.31	12.53
17h	$C_8H_5BrN_2O$	42.70	2.24	12.45	42.66	2.20	12.38
17j	$C_8H_5IN_2O$	35.32	1.85	10.30	35.51	1.91	10.22
17k	$C_8H_5IN_2O$	35.32	1.85	10.30	35.26	1.86	10.43

Synthesis of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones (17). *General Method*. Isopropylidene (2-pyridylamino)methylenemalonate (**13**) (20 g) was added to Ph_2O (180 g) preheated to 260 °C. The reaction mixture was heated at 260 °C for 10 min, then quickly cooled to room temperature, diluted with *n*-hexane (200 mL) and extracted with 2 *N* HCl. The pH of the separated aqueous phase was adjusted to 8 with 40% aqueous NaOH, and the precipitated 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**) was filtered off, washed with water, and recrystallized from EtOH. Yields and mp are given in Table 1, and results of the elemental analysis are listed in Table 5.

Cyclization of Isopropylidene (6-halo-2-pyridylamino)methylenemalonates (27). 6-Halo derivative **13l,** or **m** (2 g) was added to Ph_2O (40 g) preheated at 260 °C, the reaction mixture was heated at 260 °C for ~2 min, then quickly cooled to room temperature and diluted with *n*-hexane (80 mL). The precipitated crystals were filtered off, and **27** and **29** were separated by fractional crystallization from EtOH.

7-Chloro-1,4-dihydro-1,8-naphthyridin-4-one (27a). Yield and mp are given in Table 2. ^{1}H NMR δ 12.34 (brd, 1H, *J* = 5.9 Hz, NH), 8.44 (d, 1H, *J* = 8.3 Hz, 5-H), 7.94 (dd, 1H, *J* = 7.6 Hz and 5.9 Hz, 2-H), 7.44 (d, 1H, *J* = 8.3 Hz, 6-H), 6.12 (d, 1H, *J* = 7.6 Hz, 3-H); ^{13}C NMR δ 111.0 (C-3), 119.5 (C-4*a*), 120.3 (C-5), 138.7 (C-6), 140.8 (C-7), 150.4 (C-8*a*), 152.9 (C-2), 177,1 (C-4). *Anal*. Calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51. Found: C 53.34; H 2.63; N 15.70

7-Bromo-1,4-dihydro-1,8-naphthyridin-4-one (27b). Yield and mp are given in Table 2. *Anal*. Calcd for $C_8H_5BrN_2O$: C, 42.70; H, 2.24; N 12.45. Found: C, 42.58; H, 2.31; N, 12,56.

1-(6-Chloro-2-pyridyl)-3-[(6-chloro-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridine-2,4-dione (29a). Yield 8%, its purity was cca 95%, mp > 300 °C. HRMS *m/z*: (ESI$^+$) calcd for $C_{16}H_{10}Cl_2N_4O_2$ +H: 361.0253. Found: 361.0246 .

1-(6-Bromo-2-pyridyl)-3-[(6-bromo-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridine-2,4-dione (29b). Yield cca 6%, its purity was cca 80%, mp > 300 °C. HRMS *m/z*: (ESI$^+$) calcd for $C_{16}H_{10}Br_2N_4O_2$ +H: 448.9249. Found: 448.9253.

Synthesis of 3-Halo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (30). The respective *N*-halosuccinimide (0.11 mol) was added to a solution of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **17a** (14.6 g, 0.1 mol) in CCl_4 (200 mL), and the mixture was heated under reflux for 30 min, then filtered hot and cooled to ambient temperature, and the precipitated yellow crystals were filtered off and recrystallized from EtOH.

3-Chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (28a). Yield 86%, mp 159-160 °C. *Anal*. Calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51. Found: C, 53.45; H, 2.86; N, 15.35.

3-Bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (28b). Yield 76%, mp 137-138 °C, lit.,[29] mp 133-134 °C.

3-Iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (28c). Yield 86%, mp 142 °C. *Anal*. Calcd for $C_8H_5IN_2O$: C, 35.32; H, 1.85; N, 10.30. Found: C, 35.40; H, 1.69; N, 10.42.

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