Decarboxylation in the Synthesis of 4-Alkyl-, 4-Alkenyl- and 4-Acylpyrimidines

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Decarboxylation of allylic esters of 4-carboxypyrimidines in toluene at 111 °C in the presence of a Pd(0) catalyst, gives a mixture of a 4-alkenylpyrimidine and a pyrimidine unsubstituted in the 4-position. If the decarboxylation is carried out in the presence of benzaldehyde, then benzaldehyde is added to the 4-position. Decarboxylation of 4-carboxypyrimidines in the presence of different electrophiles, results in incorporation of the electrophile into the 4-position together with a pyrimidine unsubstituted in the 4-position. Use of microwave irradiation enhances the rate of the decarboxylations.

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Pyrimidines with a carbon substituent in the 4-position have traditionally been prepared by direct synthesis, *i.e.*, that the group to be the 4-substituent is already in place before the condensation of the pyrimidine ring [1]. The problem with this method is that the intermediate is not always easy accessible. A more flexible synthetic route is to use transition metal catalyzed coupling reactions of 4-halopyrimidines with organometallic compounds [2].

Alkylation by decarboxylation of esters is known from the Carroll reaction, which is a thermal rearrangement of allylic acetoacetates [3]. This reaction can be performed under mild conditions using palladium catalysis [4]. Palladium catalysis has also been used in decarboxylative alkylation of free β-keto acids [5]. To our knowledge alkylation by decarboxylation of esters or free acids in the presence of an electrophile is not known in the pyrimidine chemistry.

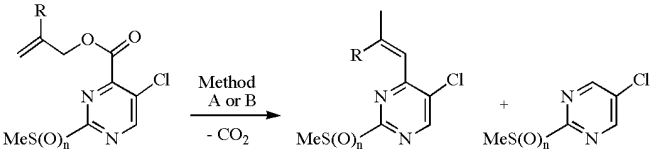
Microwave irradiation has been used to enhance the decarboxylation of organic compounds [6-8].

In this paper we report our results from decarboxylation of allylic esters of 4-carboxypyrimidines in the presence of a palladium catalyst (Table 1). The decarboxylations have also been done in the presence of benzaldehyde (Table 2). In Table 3 are presented the results from the decarboxylation of 4-carboxypyrimidines in the presence of an electrophile. Most of the decarboxylations have been carried out both pure thermally and by microwave-induction in order to make a comparison between the two methods.

Decarboxylation of allylic esters by a palladium catalyst, can occur at relatively low temperature (*i.e.*, room temperature) if a negative charge, which is presumably formed after the decarboxylation, can be delocalized into a π-system (as in the Pd-catalyzed Carroll-reaction [4]). In the decarboxylation of 4-carboxypyrimidines any carbanion that might be formed cannot be delocalized into a π-system. Thus higher temperature is needed to get decarboxylation in these systems. The exact temperature needed depends on the substituent pattern in each case, *e.g.*, 4-carboxy-5-chloro-2-methylthiopyrimidine decarboxylates around 160 °C [9] while 1,3-dimethylorotic acid decarboxylates around 200 °C [10]. We have found that allylic esters of 4-carboxy-5-chloro-2-methylthiopyrimidine can be decarboxylated in refluxing toluene in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium. Without the catalyst no decarboxylation takes place. Toluene was found to give better turn-over than a number of other solvents at the same temperature *e.g.*, anisole, benzonitrile, DMPU and DMF.

In the decarboxylation of the allylic esters of 4-carboxypyrimidines (**1**, Table 1) some pyrimidine unsubstituted in the 4-position (**3**) were always isolated together with the 4-alkenylated pyrimidine (**2**). The product distribution is readily estimated from the ^{1}H NMR spectrum of the crude product by integration over the proton in the 6-position. For example, as shown by methylthio derivatives in Table 1 and Scheme 1, the H-6 in the allylic ester **1** is observed at lowest field (**1a** 8.57, **1b** 8.57, **1d** 8.53), followed by H-6 in compound **3** (**3a** 8.45) and at highest field the H-6 in the alkenylated pyrimidine **2** (**2a** 8.35, **2b** 8.34). Similar procedures are applicable to the products in Table 2 and 3.

Table 1
Decarboxylation of Allylic Esters of 4-Carboxypyrimidines



1 **2** **3a,c**

Entry	Compound	R	n	Method [a]	Product ratio[b] **2**:**3**	Isolated yield (%) **2**	**3**
1	a	H	0	A	44:56	16	30
2	a	H	0	B	74:26	78	9
3	b	Me	0	A	87:13	68	---
4	b	Me	0	B	94: 6	72	---
5	c	Me	2	A	50:50	11	13
6	c	Me	2	B	82:18	32	---

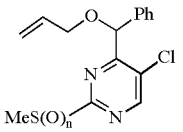
[a] Method A: 5 mol % Pd (PPh_3)$_4$, toluene, reflux, 72 h; Method B: 5 mol % Pd (PPh_3)$_4$, toluene-benzonitrile 1:1, MW, 20 min. [b] From ^{1}H NMR of the crude product.

The product distribution is dependent on the reaction conditions and on the type of allylic ester used. In the case of the allylic ester **1a** (entry 1, Table 1) under thermal conditions, pyrimidine **3a** was the main product. While in the microwave assisted reaction, decarboxylation of the same ester (entry 2) gave the alkenylated pyrimidine **2a** as the main product. The allylic ester **1b**, however, gave the alkenyllated pyrimdine **2b** as the main product both in the thermal and the microwave assisted reaction (entries 3 and 4). In the sulfone **1c** there was again a difference between the thermal and the microwave assisted reaction (entries 5 and 6). Use of microwave irradiation greatly reduced the time needed to get complete decarboxylations. The pure thermal decarboxylations at 111 °C took from 48 to 72 h, while the microwave assisted decarboxylations were complete in 20 min.

The formation of the products **3a** and **3c** (Table 1) has also to be explained. We anticipated that the required proton could come from the solvent, from water in the solvent or from the allyl part of the ester. In order to rule out any water in the solvent, the solvent was dried and distilled. In addition all the reactions were run under an atmosphere of argon. The decarboxylation was run in toluene-d_8 to check if proton donation was by the solvent. The result was no incorporation of deuterium into the 4-position. This left us with the option that the hydrogen must come from the allyl part of the ester. 1,4-Elimination from π-allyl palladium complexes to form conjugated dienes is well known [11]. Indeed the decarboxylation of the ester **1d** (Scheme 1) gave only the pyrimidine **3a** (85 %) together with isoprene [12].

ester **1a**, **1b** or **1d** was also performed in the presence of an excess of benzaldehyde. In all cases a product was obtained by 1,2 addition of the pyrimidine ring to benzaldehyde (Scheme 1 and entries 1- 4, Table 2). Alkenylation of the 4-position was also observed, but this product was always the minor product, except in the microwave assisted reaction of **1b** (entry 4). Regeneration of Pd(0) by formation of any allylated alcohol like **5** (Scheme 2) was not observed. This is somewhat surprising since allylation of alkoxides by π-allyl palladium complexes is known [14].

Scheme 2



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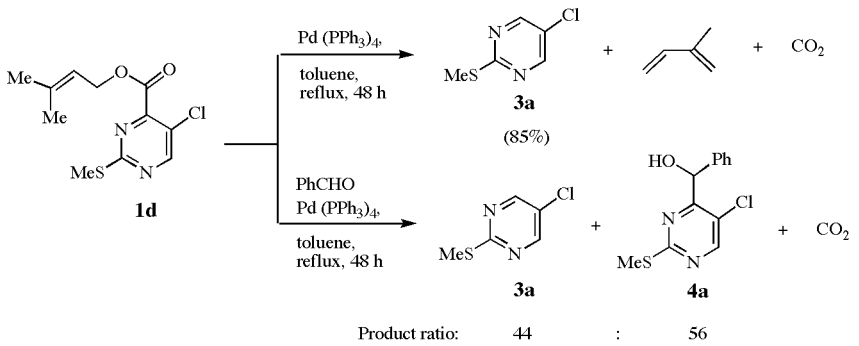
Since regeneration of Pd(0) is necessary for the catalytic cycle to work, some other mechanism must be operating. Decomposition of π-allyl palladium complexes or addition of π-allyl palladium complexes to an alkene followed by a β-elimination may be ways in which Pd(0) is regenerated. An intramolecular version of the reaction above is known from allylic esters of β-keto acids [15]. Also in this report is the mechanism for the regeneration of the catalytic species is unclear.

Scheme 1

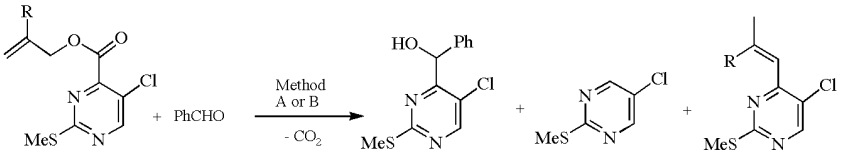


With the esters **1a** and **1b**, however, there is no possibility for formation of any conjugated diene. In the case of **1a** formation of allene from the π-allyl palladium complex would explain the formation of **3a**, while in the case of **1b** the formation of methylenecyclopropane would explain the formation of **3a**. In this context it can be mentioned that methylenecyclopropane can be prepared from β-methallyl chloride [13]. Decarboxylation of the allylic

Decarboxylation of the 4-carboxypyrimidines **6** at 115 °C in the presence of an electrophile, lead also to incorporation of the electrophile into the 4-position of the pyrimidine ring together with **3a** or **3c** (Table 3). The degree of incorporation depends on the nature of the electrophile *e.g.*, benzaldehyde being more reactive than benzophenone and benzoyl chloride. In the reaction of compounds **1a** and **1e** with benzaldehyde (entries 1, 2, 9 and 10), the

Table 2

Decarboxylation of Allylic Esters of 4-Carboxypyrimidines in the Presence of Benzaldehyde



1 **4a** **3a** **2a,b**

Entry	Compound	R	Method [a]	Product ratio [b] **4a:3a:2**	Isolated yield (%) **4a**	**3a**	**2**
1	a	H	A [c]	89: 0 :11	---	---	---
2	a	H	B [d]	62:15:23	52	6	10
3	b	Me	A	89: 0:11	67		
4	b	Me	B	40:13:47	29	---	---

a) Method A: 5 mol % Pd $(PPh_3)_4$, toluene, reflux, 72 h; Method B: 5 mol % Pd $(PPh_3)_4$, toluene-benzonitrile 1:1, MW, 20 min. b) From ^{1}H NMR of the crude product. c) Reflux 48 h, turn-over 69 %. d) 7% of compound **1a** was recovered

microwave assisted reaction gave more of the addition product **4** than that of the thermal reaction. In most other cases the use of microwave heating did not alter the product ratio to any great extent.

When 1,3-dimethylorotic acid is heated in benzyl bromide at 198 °C,the benzyl group is then incorporated into the 6-position of the pyrimidine system (10 % yield [16]). When the free acid **6a** was heated in benzyl bromide at 115 °C for 48 h only the decarboxylation product **3a** was observed.

In summary, we have demonstrated that 4-alkenylpyrimidines can be prepared through palladium catalyzed decarboxylation of allylic esters of 4-carboxypyrimidines; that 4-alkyl or 4-acylpyrimidines can be prepared by decarboxylation of 4-carboxypyrimidines in the presence of an electrophile. In addition we have shown that the reaction time can be greatly reduced by microwave irradiation.

EXPERIMENTAL

All reactions were conducted under an inert amosphere of either Ar or N_2. *N,N*-Dimethylformamide (DMF) was dried with $MgSO_4$ before distillation. Toluene was distilled from sodium and kept over molecular sieves. The ^{1}H NMR spectra were recorded at 200 or 300 MHz and the ^{13}C NMR spectra at 50 or 75 MHz on Bruker Avance DPX instruments. Mass spectra, under electron impact conditions, were recorded at 70 eV ionizing energy on a Fision ProSpec instrument. The spectra are presented as *m/z* (% rel. int.). IR spectra were recorded on a Nicolet Magna FT-IR 550 instrument. The microwave experiments were carried out using a CEM MDS-81D microwave oven at 600 – 400 W for 20 min (600 W 8 min, 500 W 6 min and 400 W 6 min). The melting points are uncorrected.

5-Chloro-2-methylthio-4-(2-propenyloxy)pyrimidine (**1a**).

3-Bromopropene (5.0 mL, 57.2 mmol) was added to a mixture of 4-carboxy-5-chloro-2-methylthiopyrimidine [9] (6.02 g, 29.4 mmol) and triethylamine (10.0 mL, 72 mmol) in CH_2Cl_2 (150 mL). The mixture was stirred for 24 h at ambient temperature before the solvent was removed. The residue was dissolved in EtOAc (50 mL), washed with water (2 x 50 mL), $NaHCO_3$(aq, sat) (50 mL) and brine (50 mL) before it was dried ($MgSO_4$). The crude product was purified by flash chromatography using silica gel. Eluent EtOAc - hexane 1:19. The compound was obtained as a yellow oil; (4.68 g, 65%); ir (neat): 1744 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.54 (3H, s, SCH_3), 4.87 (2H, dt, O-CH_2, J = 5.8 and 1.3 Hz), 5.31 (1H, dq, C=CH_a, J =10.4 and 1.1 Hz), 5.44 (1H, dq, C=CH_b, J = 17.2 and 1.1 Hz), 5.93 – 6.06 (1H, m, C=CH), 8.57(1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.4 (S-CH_3), 66.8 (O-CH_2-CH), 119.4 (C=CH_2), 123.2 (C5), 130.7 (C=CH-CH_2), 154.0 (O=C-O), 158.1 (C6), 162.3 (C4), 171.0 (C2); ms: *m/z* (EI) 246 (M^+ +2, 37%), 244 (M^+, 100%), 231 (24), 229 (66), 205 (35), 203 (99), 161 (28), 159 (68), 146 (16), 144 (39), 41 (44).

HRMS (EI) for $C_9H_9ClN_2O_2S$ requires *M*, 244.0073. Found: *m/z* 244.0079.

5-Chloro-4-(2-methyl-2-propenyloxy)-2-methylthiopyrimidine (**1b**).

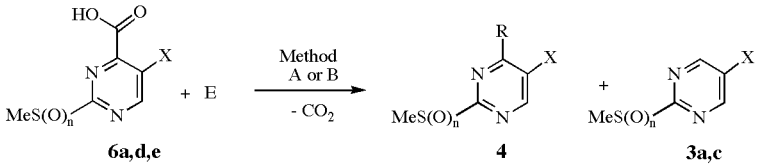
Compound **1b** was prepared as **1a** above from 4-carboxy-5-chloro-2-methylthiopyrimidine [9] (3.05 g, 14.9 mmol) and triethylamine (5.0 mL, 36 mmol) and 3-bromo-2-methylpropene (1.7 mL, 16.3 mmol) in CH_2Cl_2 (55 mL). The crude product was purified by flash chromatography using silica gel. Eluent EtOAc - hexane 1:19. The compound was obtained as a yellow oil; (2.28 g, 59%); ir (neat): 1746 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.81 (3H, s, CH_3), 2.54 (3H, s, SCH_3), 4.79 (2H, s, O-CH_2), 5. 00 (1H, m, C=CH_b, J = 0.7 Hz), 5.10 (1H, m, C=CH_a, J = 0.7 Hz), 8.57 (1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.5 (S-CH_3), 19.4 (C-CH_3), 69.6 (O-CH_2-C), 114.3 (C=CH_2), 123.2 (C5), 138.7 (C=C), 154.2 (O=C-O), 158.2 (C6), 162.5 (C4), 171.1 (C2); ms: *m/z* (EI) 260 (M^++2, 11%), 258 (M^+, 26%), 245 (37), 243 (100), 215 (16), 213(36), 162 (25), 160 (70), 146 (15), 144 (32), 55 (58).

HRMS (EI) for $C_{10}H_{11}ClN_2O_2S$ requires *M*, 258.0230. Found: *m/z* 258.0230.

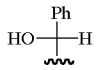
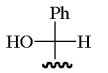
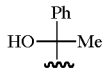
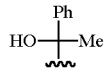
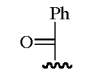
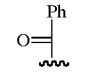
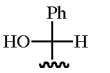
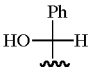
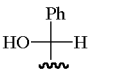
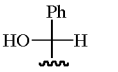
5-Chloro-4-(2-methyl-2-propenyloxy)-2-methylsulfonylpyrimidine (**1c**).

3-Bromo-2-methylpropene (2.0 mL, 19.2 mmol) was added to a mixture of 4-carboxy-5-chloro-2-methylsulfonylpyrimidine [9]

Table 3
Decarboxylation of 4-Carboxypyrimidines in the Presence of an Electrophile (E)



6a,d,e

Entry	Compound	n	X	E	Method[a]	R	Product ratio [b] **4:3**	Isolated yield (%) **4**
1	a	0	Cl	PhCHO	A		64:34	47
2	a	0	Cl	PhCHO	B		---	74 [c]
3	b	0	Cl	PhCOMe	A		26:74	23 [d]
4	b	0	Cl	PhCOMe	B		29:71	25
5	c	0	Cl	PhCOCl	A		31:69	19
6	c	0	Cl	PhCOCl	B		22:78	19
7	d	2	Cl	PhCHO	A		38:62	21
8	d	2	Cl	PhCHO	B		43:57	22
9	e	0	Br	PhCHO	A		40:60	12
10	e	0	Br	PhCHO	B		---	65 [e]

[a] Method A: 115 °C 48 h; Method B: 7 anisole, MW, 20 min. [b] From ^{1}H NMR of the crude product. [c] Compound 3a was isolated in 14% yield. [d] Compound 3a was isolated in 57% yield. [e]Compound 3a was isolated in 29% yield.

(2.00 g, 8.5 mmol) and triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (55 mL). The mixture was stirred at ambient temperature for 48 h before the solvent was evaporated off. The crude product was purified by flash chromatography using silica gel. Eluent EtOAc - hexane 1:4. The compound was obtained as a yellow oil; (2.18 g, 89%); ir (neat): 1745 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.81(3H, s, CH_3), 3.35 (3H, s, SO_2CH_3), 4.82 (2H, s, O-CH_2), 5.01(1H, s, C=CH_b), 5.09 (1H, t, C=CH_a, J = 1 Hz), 9.02 (1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 19.4 (C-CH_3), 39.4 (SO_2-CH_3), 70.4 (O-CH_2-C), 115.0 (C=CH_2), 131.6 (C5), 138.2 (C=C), 155.5 (O=C-O), 160.1 (C6), 161.2 (C4), 163.4 (C2); ms: *m/z* (CI, CH_5^+) 293(M^++2, 21%), 291 (M^+, 64%), 55 (100).

5-Chloro-4-(3-methyl-2-butenyloxy)-2-methylthiopyrimidine (**1d**).

4-Carboxy-5-chloro-2-methylthiopyrimidine [9] (5.30 g 25.9 mmol) was heated in thionyl chloride (12 mL) under reflux for 2 h. Excess thionyl chloride was removed and 3-methyl-2-buten-1-ol (7.0 mL, 68 mmol) was added dropwise before the mixture was heated at 80 °C for 3 h. The reaction mixture was dissolved in EtOAc (50 mL), washed with water (2 x 50 mL), $NaHCO_3$(aq, sat) (50 mL) and brine (50 mL) before it was dried ($MgSO_4$). The crude product was purified by flash chromatography using silica gel. Eluent EtOAc - hexane 1:19. The compound was obtained as a yellow oil; (3.58 g, 51%); ir (neat):1744 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.73 (3H, s, CH_3), 1.74 (3H, s, CH_3), 2.52 (3H, s, SCH_3), 4.85(2H, d, O-CH_2, J = 7.4 Hz), 5.39 – 5.44 (1H, tm, C=CH, J = 7.4 Hz), 8.53 (1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.4 (S-CH_3), 18.0 (C-CH_3), 25.6 (C-CH_3), 63.3 (O-CH_2-C), 117.2 (C=CH_2), 123.1(C5), 140.8 (C=C), 154.6 (O=C-O), 157.9 (C6), 162.8 (C4), 171.0 (C2); ms: *m/z* (EI) 274 (M^++ 2, 11%), 272 (M^+, 29%), 229 (6), 227 (16), 206 (25), 204 (65), 162 (19), 160 (60), 69 (100), 41 (48).

HRMS (EI) for $C_{11}H_{13}ClN_2O_2S$ requires *M*, 272.0386. Found: *m/z* 272.0375.

General Methods for Decarboxylation of Allylic Esters of 4-Carboxypyrimidines (Table 1).

Method A.

A mixture of the pyrimidine **1** (3.0 mmol) and $Pd(PPh_3)_4$ (0.15 mmol) in toluene (12 mL) under an atmosphere of argon was heated under reflux for 72 h. The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

Method B.

A mixture of the pyrimidine **1** (0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol) in toluene (1.5 mL) and benzonitrile (1.5 mL) in a teflon container (100 mL) was heated in a CEM MDS-81D microwave oven at 600 – 400 W for 20 min (600 W 8 min, 500 W 6 min and 400 W 6 min). The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

(*E*)-5-Chloro-2-methylthio-4-(1-propenyl)pyrimidine (**2a**) [17].

This compound was purified using eluent EtOAc - hexane 1:49; ^{1}H nmr (200 MHz, $CDCl_3$): δ 1.98 (3H, dd, CH_3, J = 1.7 and 6.9 Hz), 2.55 (3H, s, S-CH_3), 6.75 (1H, m, C=C-H, J = 1.7 and 15.2 Hz), 7.34 (1H, dq, C=C-H J = 7.0 and 15.2 Hz), 8.35 (1H, s, N=C-H); ms: *m/z* (EI) 202 (M^++2, 33%), 200 (M^+, 100%), 169 (29), 167 (86), 119 (22), 65 (22).

HRMS (EI) for $C_8H_9ClN_2S$ requires *M*, 200.0174. Found: *m/z* 200.0177.

5-Chloro-4-(2-methyl-1-propenyl)-2-methylthiopyrimidine (**2b**).

This compound was purified using eluent EtOAc - hexane 1:49; mp 75 - 77 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.02 (3H, d, CH_3, J = 1.2 Hz), 2.24 (3H, d, CH_3, J = 1.2 Hz), 2.53 (3H, s, S-CH_3), 6.48 (1H, m, C=C-H, J = 1.2 Hz), 8.34 (1H, s, N=C-H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.6 (S-CH_3), 21.1 (=C-CH_3), 28.5 (=C-CH_3), 118.3 (C=CH), 124.4 (C5), 151.4 (HC=C-$(CH_3)_2$), 156.1 (C6), 160.4 (C4), 169.4 (C2); ms: *m/z* (EI) 216(M^++2, 37%), 214 (M^+, 100%), 201 (13), 199 (38), 183 (16), 181 (54).

HRMS (EI) for $C_9H_{11}ClN_2S$ requires *M*, 214.0331. Found: *m/z* 214.0327.

5-Chloro-4-(2-methyl-1-propenyl)-2-methylsulfonylpyrimidine (**2c**).

This compound was purified using eluent EtOAc - hexane 3:7; mp 111 - 117 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.08 (3H, d, CH_3, J = 1.2 Hz), 2.33 (3H, d, CH_3, J = 1.2 Hz), 3.31 (3H, s, S-CH_3), 6.63(1H, m, C=C-H, J = 1.2 Hz), 8.68 (1H, s, N=C-H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.5 (=C-CH_3), 29.1 (=C-CH_3), 39.3 (SO_2-CH_3), 117.1(C=CH), 131.0 (C5), 156.8 (HC=C-$(CH_3)_2$), 157.1 (C6), 161.9 (C4), 162.6 (C2); ms: *m/z* (CI, CH_5^+): 249 (MH^++2, 35%), 247 (MH^+, 100%), 169 (5), 167 (19).

HRMS (CI) for $C_9H_{11}ClN_2O_2S(H^+)$ requires *M*, 247.0302. Found: *m/z* 247.0302.

General Methods for Decarboxylation of Allylic Esters of 4-Carboxypyrimidines in the Presence of Benzaldehyde (Table 2).

Method A.

A mixture of the pyrimidine **1** (1.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol) and benzaldehyde (1.0 mL, 10 mmol) in toluene (4 mL) under an atmosphere of argon was heated under reflux for 72 h. The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

Method B.

A mixture of the pyrimidine **1** (0.5 mmol), $Pd(PPh_3)_4$ (0.025 mmol) and benzaldehyde (1.0 mL, 10 mmol) in toluene (1.5 mL) and benzonitril (1.5 mL) in a teflon container (100 mL) was heated in a CEM MDS-81D microwave oven at 600 – 400 W for 20 min (600 W 8 min, 500 W 6 min and 400 W 6 min). The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

5-Chloro-2-methylthiopyrimidine (**3a**)[9].

This compound has ^{1}H nmr (300 MHz, $CDCl_3$) δ 2.52 (3H, s, S-CH_3), 8.45 (2H, s, N=C-H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 14.4 (SCH_3), 126.4 (C5), 155.5 (C4 and C6), 170.7 (C2).

5-Chloro-2-methylsulfonylpyrimidine (**3c**)[9].

This compound has ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.34 (3H, s, SO_2CH_3), 8.87 (2H, s, N=C-H).

4-(α-Hydroxybenzyl)-5-chloro-2-methylthiopyrimidine (**4a**).

This compound was purified using eluent EtOAc - hexane 1:9; mp 93 - 95 °C; ir (neat): ^{1}H nmr (200 MHz, $CDCl_3$): δ 2.60 (3H, s, SCH_3), 4.69 (1H,d, HO-C-H, J = 7.9 Hz), 5.89 (1H, d, H-C-OH, J = 7.9 Hz), 7,27 – 7.35 (5H, m, Ar), 8.37(1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$) δ 14.5 (S-CH_3), 71.8 (H-C-OH), 123.8 (C5), 127.4, 128.4, 128.6, 139.7 (Ar), 156.6 (C6), 165.4 (C4), 170.2 (C2); ms: *m/z* (EI) 268 (M^++2, 34%), 266 (M^+, 100%), 217 (6), 215 (22), 162 (11), 160 (28), 77(47).

HRMS (EI) for $C_{12}H_{11}ClN_2OS$ requires *M*, 266.0281. Found: *m/z* 266.0285.

General Methods for Decarboxylation of 4-Carboxypyrimidines in the Presence of an Electrophile (Table 3).

Method A.

A mixture of the 4-carboxypyrimidine **6** (2.0 mmol) and the electrophile (5.0 mL) under an atmosphere of argon was heated under reflux for 48 h. The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

Method B.

A mixture of the 4-carboxypyrimidine **6** (0.5 mmol) and the electrophile (1.0 mL) in anisole (2.0 mL) in a teflon container (100 mL) was heated in a CEM MDS-81D microwave oven at 600 – 400 W for 20 min (600 W 8 min, 500 W 6 min and 400 W 6 min). The solvent was evaporated off and the crude product purified by flash chromatography on silica gel.

4-(1-Hydroxy-1-phenylethyl)-5-chloro-2-methylthiopyrimidine (**4b**).

This compound was purified using eluent EtOAc - hexane 1:9. The compound was obtained as a yellow oil; ir (neat): 3416 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.00 (3H, s, C-CH_3), 2.61 (3H, s, SCH_3), 5.62 (1H, s, C-OH), 7.25 – 7.32 (5H, m, Ar), 8.34 (1H, s, N=C-H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.6 (S-CH_3), 25.2 (C-CH_3), 75.3 (HO-C-CH_3), 123.8 (C5), 126.4, 127.7, 128.2, 143.0 (Ar), 158.3 (C6), 168.1 (C4), 169.3 (C2); ms: *m/z* (EI) 282 (M^++2, 37%), 280 (M^+, 100%), 267 (5), 265 (16), 162 (17), 160 (46), 121 (65).

HRMS (EI) for $C_{13}H_{13}ClN_2OS$ requires *M*, 280.0437. Found: *m/z* 280.0437.

4-Benzoyl-5-chloro-2-methylthiopyrimidine (**4c**).

This compound was purified using eluent EtOAc - hexane 1:9; mp 96 – 104 °C; ir (neat): 1682 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 2.51(3H, s, SCH_3), 7.46 – 7.85(5H, m, Ar), 8,60 (1H, s, N=C-H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.6 (S-CH_3), 122.8 (C5), 128.9, 130.2, 133.9, 134.7 (Ar), 157.5 (C6), 160.8 (C4), 171.0 (C2), 190.2 (C=O); ms: *m/z* (EI) 266 (M^++2, 15%), 264 (M^+, 43%), 267 (5), 105 (100), 77 (59), 51 (17).

HRMS (EI) for $C_{12}H_9ClN_2OS$ requires *M*, 264.0124. Found: *m/z* 264.0123.

4-(α-Hydroxybenzyl)-5-chloro-2-methylsulfonylpyrimidine (**4d**).

This compound was purified using eluent EtOAc - hexane 3:7. The compound was obtained as a yellow oil; ir (neat): 3462 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 3.35 (3H, s, SO_2CH_3), 4.60 (1H, d, HO-C-H, J = 5.0 Hz), 6.08 (1H, d, H-C-OH, J = 5.0 Hz), 7.28 – 7.37 (5H, m, Ar), 8,73(1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 39.5 (SO_2-CH_3), 72.4 (H-C-OH), 127.4, 128.9, 128.9 (Ar), 131.7 (C5), 138.5 (Ar), 157.7 (C6), 163.1 (C4), 168.7 (C2);ms: *m/z* (ESI, Na^+) 323 (MNa^++2, 50%), 321 (MNa^+, 100%), 301 (5), 299 (14), 283 (13), 281(38).

HRMS (ESI, Na^+) for $C_{12}H_{11}ClN_2O_3S(Na^+)$ requires *M*, 321.0071. Found: *m/z* 321.0056.

4-(α-Hydroxybenzyl)-5-bromo-2-methylthiopyrimidine (**4e**).

This compound was purified using eluent EtOAc - hexane 1:9; mp 107 – 112 °C; ir (neat): 3436 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 2.59 (3H, s, SCH_3), 5.85 (1H , s, HO-C-H) 7.27 – 7.36 (5H, m, Ar), 8.48 (1H, s, N=CH); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.5 (S-CH_3), 73.2 (H-C-OH), 113.4 (C5), 127.7, 128.4, 128.6, 139.7 (Ar), 159.1 (C6), 166.6 (C4), 170.9 (C2); ms: *m/z* (EI) 312 (M^++2, 55%), 310 (M^+, 61%), 206 (16), 204 (13), 105 (40), 77 (100), 51 (20).

HRMS (EI) for $C_{12}H_{11}BrN_2OS$ requires *M*, 309.9775. Found: *m/z* 309.9789.

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