A Facile Synthesis of 5-Halopyrimidine-4-Carboxylic Acid Esters via a Minisci Reaction

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Received 28 October 2011

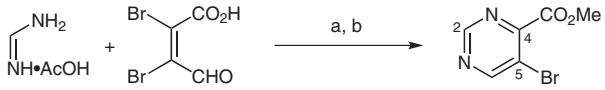
Abstract: This paper reports the synthesis of various 5-halopyrimidine-4-carboxylic acid esters via the Minisci homolytic alkoxycarbonylation of 5-halopyrimidines. The reaction was found to be highly regioselective, allowing the one-step synthesis of useful amounts (>10 g) of ethyl 5-bromopyrimidine-4-carboxylate where other methods proved difficult. Ethyl 5-bromopyrimidine-4-carboxylate was used for the preparation of potent CK2 inhibitors including CX-5011. This work represents an interesting application of radical chemistry for the preparation of pharmacologically active molecules.

Key words: Minisci reaction, alkoxycarbonylation, radicals, pyrimidine, antitumor agents

Pyrimidines are ubiquitous heterocycles found across a wide range of biologically active molecules, including various marketed drugs such as Gleevec®[1] (oncology), Etravirine®[2] (virology), and Trimethoprim[3] (antibacterial), among others.[4] Novel methods to synthesize functionalized pyrimidines are therefore extremely useful for medicinal chemists. We recently described the discovery of a novel class of potent inhibitors of protein kinase CK2, of which the analogue CX-5011 (Scheme 1) displayed in vivo analgesic properties.[5] Structure–activity relationship (SAR) studies showed that the pyrimidine ring of CX-5011 was a key structural element responsible for the remarkably high potency and selectivity of the drug.[6]

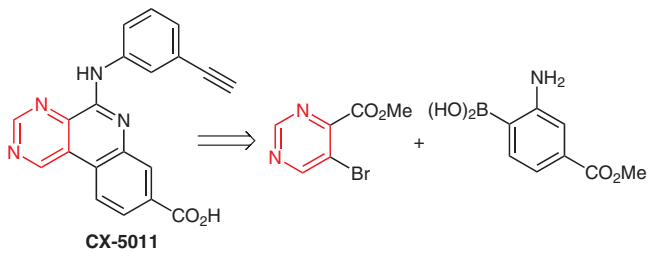
The synthesis of the tricyclic pyrimido[4,5-*c*]quinoline core of CX-5011 involved a domino Suzuki coupling–intramolecular amide formation between methyl 5-bromopyrimidine-4-carboxylate and the commercially available 2-amino-4-(methoxycarbonyl) phenylboronic acid.[7] Although efficient, this route suffered from the limited commercial availability and high price of methyl 5-bromopyrimidine-4-carboxylate, prompting us to develop a simple preparation of this key intermediate.

The synthesis of this intermediate by a patent procedure[8] was repeatedly low yielding in our hands (Scheme 2). The condensation of formamidine acetate and mucobromic acid upon heating in alkaline media produced 5-bromopyrimidine-4-carboxylate accompanied by a large amount of unknown byproducts. Formation of the methyl ester via the acid chloride followed by a laborious chromatographic purification furnished our desired intermediate in an overall yield ranging from 3–8% over two steps (starting from 50–100 g of mucobromic acid).



Scheme 2 *Reagents and conditions*: (a) EtONa, EtOH, 50 °C (b) $(COCl)_2$, CH_2Cl_2, cat. DMF, r.t., then MeOH, 3–8% over two steps.

Attempts to find a more efficient route through functional-group interconversions from commercially available pyrimidines were unsuccessful. In particular, the regioselective magnesiation[9] or lithiation[10,11] of 5-bromopyrimidine and subsequent reaction with dimethyl carbonate or methyl chloroformate failed to provide any detectable amount of methyl 5-bromopyrimidine-4-carboxylate.



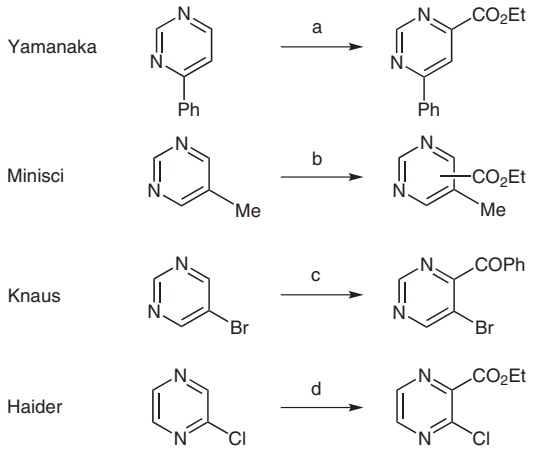
Scheme 1 Structure of CX-5011 and its retrosynthetic precursors

SYNLETT 2012, 23, 443–447
Advanced online publication: 19.01.2012
DOI: 10.1055/s-0031-1290136; Art ID: S60711ST

We turned our attention toward the direct alkoxycarbonylation of 5-substituted pyrimidines via a Minisci reaction.[12–15] Surprisingly, few Minisci-type transformations involving pyrimidines have been described in the literature, stimulating our further exploration of the scope of this reaction. Herein, we report our investigation and the facile preparation of the compound of interest.

Our strategy initially raised concerns about regioselectivity and the possibility of polysubstitutions of the pyrimidine ring. Although numerous reports of homolytic alkoxycarbonylations of pyridines and other heterocycles have been previously described,[12,16–19] only two papers have reported the use of pyrimidines as substrates for the same reaction. Yamanaka et al. (Scheme 3)[20] described the regioselective homolytic ethoxycarbonylation of 4-phenyl pyrimidine. The reported yield was low (17%), and the substrate benefited from a phenyl group occupying one of the other possible sites for substitution. Minisci et al.[19] reported the ethoxycarbonylation of 5-methylpyrimidine in excellent conversion (94%) and isolated yield (83%), but with a moderate regioselectivity (2- vs. 4-substitution = ca. 2:1).

The homolytic benzoylation of 5-bromopyrimidine reported by Knaus et al.[21] caught our attention because of its selectivity for the desired 4-position on a substrate identical to ours, and a good yield (61%) on a 40-gram scale. Finally, another example of selective ethoxycarbonylation on 2-chloropyrazine was reported by Haider et al.[22] in a synthetically useful yield (56%), increasing our confidence in the approach.

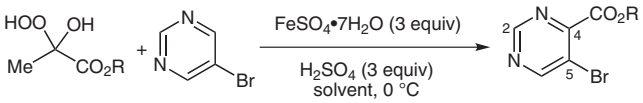


Scheme 3 Relevant literature examples of homolytic addition of carbonyl radicals to two-heteroatom heterocycles. *Reagents and conditions*: (a) ethyl pyruvate, 30% H_2O_2, $FeSO_4·7H_2O$, H_2SO_4, H_2O, 17%;[20] (b) CO_2EtCO_2H, $Na_2S_2O_8$, $AgNO_3$, CH_2Cl_2–H_2O, 83%;[19] (c) *t*-BuOOH, $FeSO_4·7H_2O$, benzaldehyde, H_2SO_4, AcOH–H_2O, 61%;[21] (d) ethyl pyruvate, 30% H_2O_2, $FeSO_4·7H_2O$, H_2SO_4, toluene–H_2O, 56%.[22]

Because the first alkoxycarbonylation increases the electrophilicity of the substrate,[15] polysubstitutions are typically observed. Polysubstitutions were observed during the acylation of a 4,6-disubstituted pyrimidine,[23] but not during the homolytic benzoylation of 5-bromopyrimidine by Knaus et al.[21] The 4-acylated product was isolated in 61% yield on a 40-gram scale with no polysubstituted products present, despite three possible sites for substitution. In a separate paper, Heinisch and Lotsch used a biphasic dichloromethane–water solvent system to suppress polysubstitution by partitioning the more lipophilic product into the organic layer, whereas the more hydrophilic protonated heterocycle preferred the aqueous phase where the substitution occured.[16]

For our initial experiments (Table 1, entry 1), we used the conditions of Haider[22] in a toluene–water biphasic system. The alkoxycarbonyl radical was generated by Fe(II)-mediated redox decomposition of 2-hydroperoxy-2-hydroxypropanoates which were formed separately by treating various alkylpyruvates with hydrogen peroxide prior to their addition to the reaction mixture. These conditions resulted in a gratifyingly high selectivity for the desired 4-position. Less than 3% of other possible isomers were detected by GC–MS, as well as a minimal amount of disubstituted product (3% of the total converted material). The conversion for the reaction (Table 1, entry 1) was high (85%), and the methyl ester was isolated in 44% yield after purification. The same reaction performed with ethyl pyruvate (Table 1, entry 2) resulted in higher conversion (89%) and isolated yield (62%) of the ethyl ester, prompting us to use this reagent for the rest of the studies.[24] Other solvents (Table 1, entries 3–5) gave similar results with the exception of water alone (Table 1, entry 5) which significantly decreased the conversion rate.

Table 1 Effect of Solvent on Conversion of 5-Bromopyrimidine to Methyl and Ethyl-5-bromo-4-carboxylates

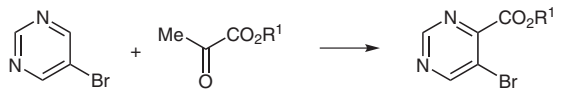


Entry	R	Solvent	Conversion (%)[a]	Product (%)[b]	Yield (%)[c]
1	Me	toluene–H_2O	85	75	44
2	Et	toluene–H_2O	89	81	62
3	Et	CH_2Cl_2–H_2O	83	81	n.d.
4	Et	AcOH–H_2O	87	56	n.d.
5	Et	H_2O	31	29	n.d.

[a] Expressed by the disappearance (GC–MS) of 5-bromopyrimidine.
[b] GC–MS peak surface area ratio of product/byproducts.
[c] Isolated yield after flash chromatography. Reactions were typically performed on a 2-mmol scale.

We subsequently explored other pyruvates (Table 2) that were not previously examined in Minisci reactions. While the methyl, ethyl, and isopropyl analogues all gave high conversions, isoamyl pyruvate (Table 2, entry 3) resulted in a lower conversion, as a result of a low miscibility with

Table 2 Homolytic Alkoxycarbonylation of 5-Bromopyrimidine Using Various Pyruvates



Entry	R^1	Conversion – no AcOH (%)[a]	Conversion – added AcOH (%)[a]	Yield (%)[b]
1	Me	85	–	44
2	Et	89	–	62
3	*i*-amyl	35	–	n.d.
4	*i*-amyl	–	100	75
5	i-Pr	98	95	60
6	Bn	–	96	33[c]

[a] Expressed by the disappearance (GC–MS) of 5-bromopyrimidine.
[b] Isolated yield after chromatography.
[c] No benzyl ester product was formed, the yield given is of the benzyl radical adduct 4-benzyl-5-bromopyrimidine.

the hydrogen peroxide–water used to prepare the radical precursor.

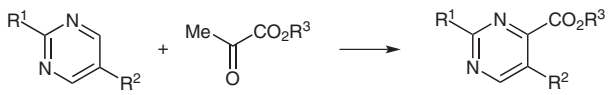
This was solved by the use of acetic acid as a co-solvent during this stage, resulting in a significant increase in conversion rate (35–100%) and the highest of all yields (75%). Acetic acid has been previously used to solubilize lipophilic aldehydes in related homolytic acylations.[14,25] In our studies, acetic acid was also used with the isopropyl and benzyl pyruvates (Table 2, entries 5 and 6). The isopropyl pyruvate formed an appreciable amount of alkylation substitution products (ca. 12% of the converted material), which was not unexpected in view of precedent literature descriptions of decarbonylation and decarboxylations of various acyl radicals.[19,21,25,26] It became the dominant pathway in the case of benzyl pyruvate which led exclusively to the formation of the benzyl-substituted product (Table 2, entry 6).

The effect of acetic acid on the conversion was further investigated on several substrates and pyruvates (Table 3). In nearly all cases the addition of acetic acid increased the conversions of the alkoxycarbonylation.

Having settled on the standard conditions,[27] we set forth to explore further the scope of the Minisci ethoxycarbonylation on diversely substituted pyrimidines (Table 4). Various 5-halogen substituents were examined (Table 4, entries 1–3) and generally displayed high conversions. Substrates bearing various synthetic handles on the 2-position, useful for SAR purposes, were examined (Table 4, entries 4–11). The substrates bearing electron-withdrawing groups (EWG) at the 2-position gave low conversions (Table 4, entries 4, 5, 7–9) while substrates with electron-donating groups (EDG, Table 4, entries 10–14) at the same position gave much higher conversions (>60%), with the exception of the methylthio compound (Table 4, entry 6). The 4-substitution results (Table 4, entries 15–19) paralleled the 2-substitution results, with EWG inducing poor conversions (Table 4, entries 15–17) and EDG (Table 4, entries 18, 19) inducing much higher conversions.

These observations might be the result of various protonation states of the pyrimidine ring dependent on the electronic properties of the substrate. It is widely acknowledged that the Minisci reaction requires a protonated heterocycle for the successful attack by the nucleo-

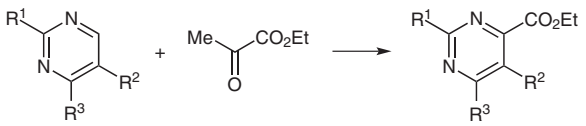
Table 3 Effect of Acetic Acid on the Conversion of Minisci Reactions between Various Pyruvates and Substituted Pyrimidines



Entry	R^1	R^2	R^3	Conversion – no AcOH (%)[a]	Conversion – with AcOH (%)[a]
1	H	Br	Me	85	94
2	H	Br	Et	89	100
3	H	Br	*i*-Pr	98	95
4	H	Br	*i*-amyl	35	100
5	H	Cl	Me	91	93
6	H	Cl	Et	91	100
7	H	I	Me	66	82
8	H	I	Et	98	99
9	MeO	Br	Et	50	68
10	*N*-pyrrolidine	Br	Et	41	62

[a] Expressed by the disappearance (GC–MS) of starting pyrimidine.

Table 4 Homolytic Ethoxycarbonylation of Diversely Substituted Pyrimidines



Entry	R^1	R^2	R^3	Conversion (%)[a,b]	Yield (%)[c]
1	H	Br	H	100 (92)	74, 48[d]
2	H	Cl	H	100 (83)	74
3	H	I	H	99 (90)	50
4	Cl	Br	H	15 (6)	–
5	F	Br	H	8 (5)	–
6	SMe	Br	H	4 (4)	–
7	SO_2Me	Br	H	8 (0)	–
8	CO_2Me	Br	H	23 (19)	–
9	CN	Br	H	7 (0)	–
10	Me	Br	H	96 (82)	52
11	NH_2	Br	H	79 (65)	25
12	NH*i*-Pr	Br	H	86 (62)	36
13	*N*-pyrrolidine	Br	H	62 (55)	15
14	OMe	Br	H	68 (58)	46
15	H	Cl	Cl	17 (13)	–
16	H	Br	CO_2Me	9 (8)	–
17	H	Br	Ph	4 (4)	–
18	H	Br	Me	86 (77)	65
19	H	Br	NH_2	97 (80)	40

[a] Conversion, expressed by the disappearance (GC–MS) of starting material.
[b] Number in parentheses is product (%), a GC–MS peak surface area ratio of product/byproducts.
[c] Isolated yield after chromatography. All reactions were performed on a 2-mmol scale.
[d] Performed on a 100-mmol scale.[27]

philic alkoxycarbonyl radical.[12] An EWG at the 2-position may prohibit protonation of the weakly basic 5-bromopyrimidine core whereas an EDG increases the basicity of the pyrimidine allowing protonation to occur and substitution to take place. Finally, it is noteworthy that the regioselectivity was high in all the examples of Table 4. The 2-isomer was either undetected or present in quantities smaller than 3%, as measured by GC–MS.

In summary, we have developed a novel and practical synthesis of 5-halopyrimidine-4-carboxylic acid esters via the Minisci alkoxycarbonylation of 5-halopyrimidines. Methods for the preparation of these molecules are rare in the literature, especially for analogues unsubstituted at the 2-position. The homolytic approach has proven a good alternative strategy to the more conventional methods such as described in Scheme 2, by reducing the number of steps and increasing the yield. Useful quantities (>10 g) of ethyl 5-bromopyrimidine-4-carboxylate were successfully synthesized in 48% yield in one step from inexpensive 5-bromopyrimidine.[27] The reaction was surprisingly regioselective, polysubstitution was minimized using a toluene–water biphasic solvent system, and the addition of acetic acid was found to increase the conversion. Our work represents a notable example of radical chemistry applied to the preparation of pharmacologically active molecules.

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(24) Methyl pyruvate typically gave conversions and isolated yields that were inferior (ca. 10–20% lower) to ethyl pyruvate on a variety of tested substrates. This had no practical consequences on the preparation of the target molecule CX-5011, where no significant differences were observed when using the methyl or the ethyl ester as a starting material.
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(27) **Typical Procedure for the Synthesis of Ethyl 5-bromopyrimidine-4-carboxylate**
In a 250 mL round-bottom flask, ethyl pyruvate (4.5 equiv, 50 mL, 450 mmol) was cooled to –10 °C. AcOH (70 mL) was added while maintaining the internal temperature below –5 °C. A 30% aq H_2O_2 solution (3 equiv, 34 g, 300 mmol) was added dropwise while maintaining the internal temperature below –2 °C. In a separate two-neck 2 L round-bottom flask fitted with a mechanical stirrer was charged 5-bromopyrimidine (1.0 equiv, 15.90 g, 100 mmol), toluene (300 mL), and H_2O (70 mL). This solution was cooled to –10 °C, and concentrated H_2SO_4 (3 equiv, 16 mL, 300 mmol) was added followed by $FeSO_4 \cdot 7H_2O$ (3.05 equiv, 84.79 g, 305 mmol). To this reaction mixture under vigorous stirring was added the peroxide solution over 1 h, while keeping the internal temperature below 0 °C. Once the addition was complete, the reaction mixture was stirred for 30 min and then decanted onto ice water (200 mL). The pH was adjusted to 7 by the addition of 1 N NaOH, and the solution was filtered over a pad of Celite and washed with CH_2Cl_2 (1 L). The aqueous layer was extracted with CH_2Cl_2 (2 × 800 mL). The organics were washed with 5% $NaHSO_3$ (2 × 500 mL), brine (1.5 L), and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (10% EtOAc–hexanes) to give a slightly yellow oil (12.49 g, 54%, >90% pure). Vacuum distillation (bp, 75–76 °C, ca. 1 mm Hg) provided analytically pure ethyl 5-bromopyrimidine-4-carboxylate as a clear, colorless oil (11.18 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 9.00 (s, 1 H), 4.51 (q, *J* = 7.2 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 161.0, 156.5, 155.8, 117.7, 62.9, 14.0 ppm. LC–MS (ES): >95% pure, *m/z* 185 $[M - OEt]^+$. GC–MS (EI): >99% pure, *m/z* = 230. The structure of the material was confirmed by its successful use in the next chemical step on route to CX-5011. All other examples described in this paper were prepared with a similar procedure, typically on a 2-mmol scale. In cases involving poorly soluble pyrimidines, H_2SO_4 was added without external cooling, with the resulting exotherm dissolving the organic substrate. The solution was then cooled to –10 °C prior to carrying on the rest of the reaction. Compounds were purified by flash chromatography on silica gel (eluting with 10% EtOAc in hexanes or 2.5% MeOH in CH_2Cl_2) and found to be 95% pure by GC–MS. All compounds isolated were characterized by ^{1}H NMR, ^{13}C NMR, and GC–MS.