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Rate Acceleration of Nucleophilic Substitution of 2-Chloro-4,6-dimethoxypyrimidine by Sulfinate Catalysis

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Abstract—The use of sulfinates greatly enhances the rate of substitution in the reaction of 2-chloro-4,6-dimethoxypyrimidine with alkoxy or aryloxy nucleophiles. Pyrimidinyloxy derivatives as intermediates for potent herbicides have been prepared in good yields from the readily available 2-chloro-4,6-dimethoxypyrimidine.

Introduction

Nitrogen heterocycles are extremely versatile building blocks for the manufacture of active compounds such as herbicides, fungicides or insecticides in the agrochemical industry. Among these, pyrimidinyloxy salicylic acids and close analogues[1–4] **1** to **3** (Fig. 1) represent a new class of compounds exhibiting potent herbicide activity by inhibition of the enzyme acetolactate synthase in plants.[5]

Seeking a direct access to the pyrimidinyloxy derivative **4** (Fig. 2), we estimated that 2-chloro-4,6-dimethoxypyrimidine (**5**) was an attractive precursor[6] since it is readily available and relatively cheap.

The nucleophilic displacement at electron-deficient heteroatomic halides is one of the most common methods to prepare the corresponding alkoxy or aryloxy derivatives. However, this straightforward approach suffers from a major drawback: the low reactivity of the 2-chloropyrimidine **5** toward nucleophilic substitution. For this reason different strategies have been developed to overcome the problem.

Most of the substitution reactions described in the literature[6–8] follow pathway A (Scheme 1) starting from the pyrimidinylsulfone **7a**, due to its good reactivity toward nucleophilic substitution. 2-Methanesulfonyl-4,6-dimethoxypyrimidine (**7a**) is usually prepared by oxidation of the methylthiopyrimidine **8**.[9] The latter can be either obtained in three steps from 4,6-dihydroxy-2-pyrimidinethiol (**9**) by successive methylation, chlorination and methoxy substitution;[10] or in a shorter route, by nucleophilic substitution of 2-chloro-4,6-dimethoxypyrimidine (**5**) with a thiolate.[11]

Despite the very good reactivity of 2-methanesulfonyl-4,6-dimethoxypyrimidine (**7a**), this pathway has two important drawbacks: the multistep synthesis to the pyrimidinylsulfone **7a** and the resulting waste situation which make this process economically and ecologically less attractive.

As already mentioned, the easy access to the chloropyrimidine

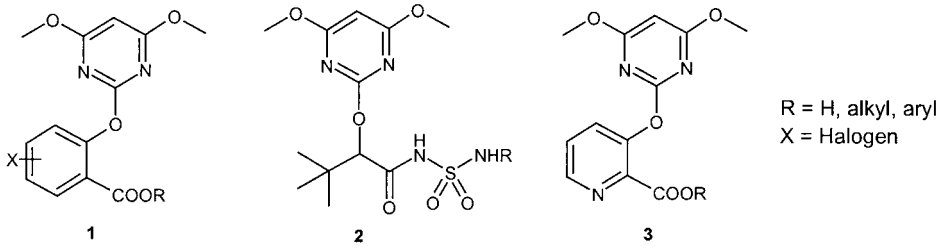

Figure 1. Pyrimidinyloxy salicylic acids and close derivatives as potent herbicides.

Keywords: aromatic nucleophilic substitution; pyrimidines; sulfinates.

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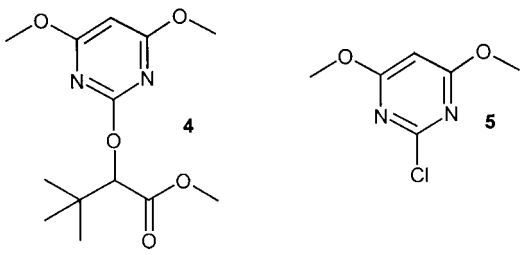


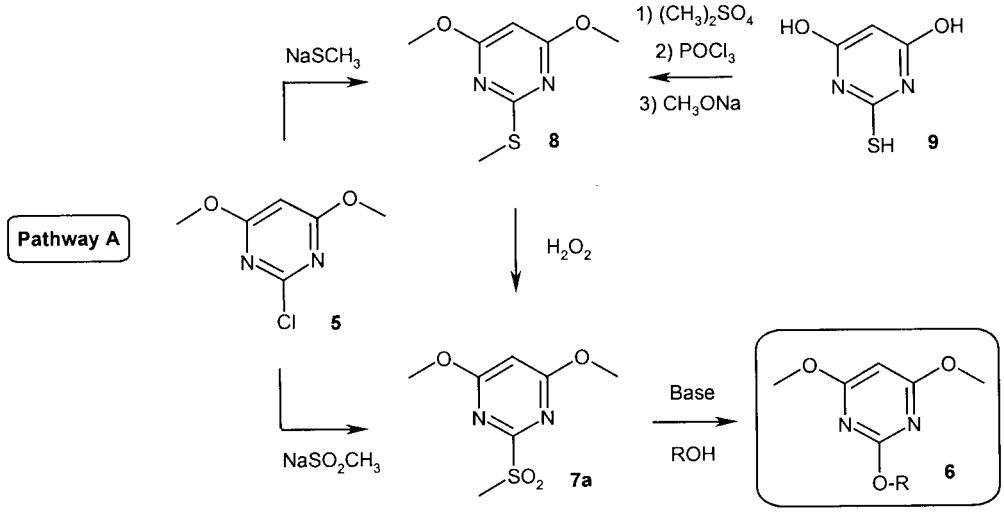
Figure 2. Pyrimidinyloxy derivative **4**, from 2-chloro-4,6-dimethoxypyrimidine (**5**).

5 is counterbalanced by its intrinsic low reactivity (pathway B). Only reactions with non-hindered phenol derivatives perform well. Indeed, the substitution reaction of a chloroheteroarene often fails or proceeds in the slow formation of the heteroarene substituted product. Another problem arises when the substitution is performed with an alkoxide (Scheme 2), typically with strong nucleophiles or under strong basic conditions: the competition between the desired substitution of the alkoxide at the 2-position, and the competitive substitution at the 4- and (or) 6-position of the pyrimidine ring.

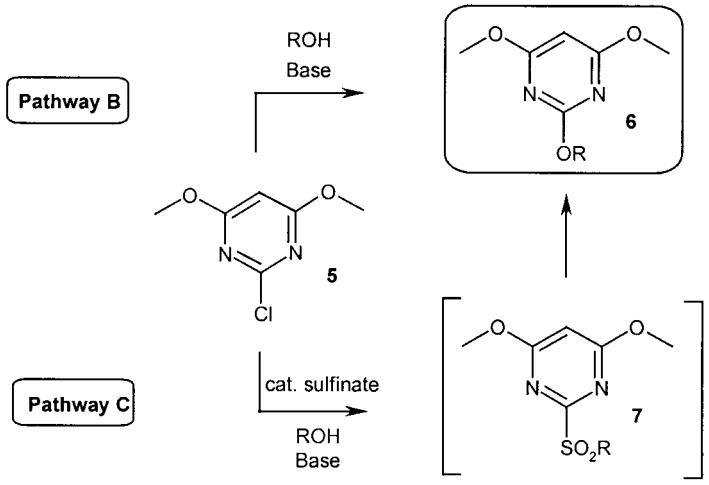
We recently found that substitution reactions can be performed in presence of a catalytic amount of an alkyl- or arylsulfinate (Scheme 3).[12] The pyrimidinylsulfone **7** is not isolated but converted in situ to the desired pyrimidinyloxy derivative **6** (pathway C). This approach combines the advantages of all other pathways, the use of the chloropyrimidine **5**, which is readily available from malonodinitrile,[11,13] the good reactivity due to the presence of the catalyst and the technically easy procedure. 2-Chloro-4,6-dimethoxypyrimidine (**5**) can thus be viewed as an economically and ecologically attractive substitute for **7** and provides a short access to a wide range of herbicides or related intermediates. A similar approach was successfully described for the substitution of chloropurines by a cyanide nucleophile.[14]

Results and Discussions

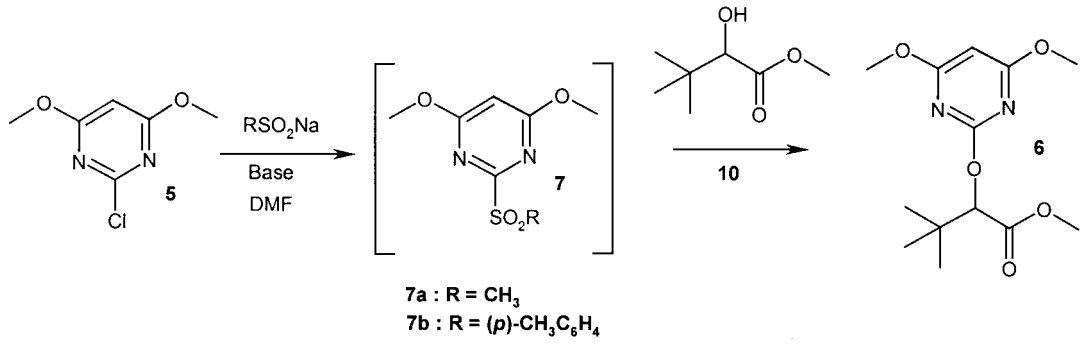
The reaction of 2-chloro-4,6-dimethoxypyrimidine (**5**) and methyl 2-hydroxy-3,3-dimethylbutanoic acid (**10**) (Scheme 3) has been chosen as a model reaction to study the catalytic effect of sulfinates under different reaction conditions. As will be demonstrated, there is a large increase of the reaction



Scheme 1. Pathway A for the synthesis of pyrimidinyloxy derivatives.

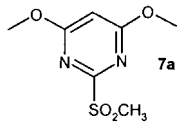
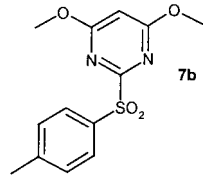
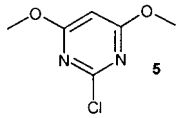
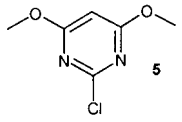


Scheme 2. Pathways B and C for the synthesis of pyrimidinyloxy derivatives.



Scheme 3. Model reaction for the parameters study.

Table 1. Effect of sulfinate in the preparation of pyrimidinyloxy derivative **6**

Entry	Starting pyrimidine	Reaction conditions[a]	Yield (%)[b] [**6**]
1	 **7a**	60°C/3 h	94
2	 **7b**	100°C/5 h	81
3	 **5**	120°C/3 h[c]	83
4	 **5**	120°C/21 h[d]	52

[a] Reaction carried out in DMF with 1.5 equiv. of potassium carbonate.
[b] Isolated yield of methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-dimethylbutanoate (**6**).
[c] Reaction carried out with 0.25 equiv. of sodium methanesulfinate.
[d] Reaction carried out without sulfinate catalysis.

rate as well as a significant increase of yield by the use of sulfinate catalysts. The reaction parameters are discussed in this section.

Reactions with isolated sulfone intermediates

To demonstrate the efficiency of the method, methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-dimethylbutanoate (**6**) was prepared from the isolated pyrimidinylsulfones **7a** and **7b** (Table 1). As expected, very good yields were obtained: 94% yield from **7a** (Entry 1) and 81% yield from **7b** (Entry 2). When the reaction was carried out directly from 2-chloro-4,6-dimethoxypyrimidine (**5**), the yield was only 52% under more drastic reaction conditions (120°C/21 h) (Entry 4). Formation of the pyrimidinylsulfone **7a** in situ from 2-chloro-4,6-dimethoxypyrimidine (**5**) in the presence of a catalytic amount of sodium methanesulfinate gave a comparable yield (83%) to that obtained using the isolated sulfone (Entry 3).

Thus, there is no need to prepare and isolate the intermediate **7**. The pyrimidinyloxy derivative **6** can be obtained directly from the chloropyrimidine **5** with a catalytic amount of sulfinate in one pot.

Parameters study

The nature of the pyrimidinylsulfone intermediate **7**, which depends on the sulfinate used for the catalysis (Scheme 3), has an influence on the reactivity. Thus, the use of sodium methanesulfinate allows a higher yield and a faster reaction compared to sodium *p*-toluenesulfinate, which forms by comparison with **7a**, a more hindered intermediate **7b**, consequently less reactive.

The use of the sulfinate has not only an influence on the reaction rate but also on the yield. Indeed, stability studies have shown that the pyrimidinyloxy derivative **6** as well as the alcohol **10**, are progressively degraded under the reaction conditions. It is therefore very important to carry out the reaction as fast as possible to minimize the decomposition of the product and the alcohol **10**. Such conditions are obtained when the substitution is catalyzed with sodium methanesulfinate (Table 2, Entry 3). The maximum conversion is reached after 2 h and methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-dimethylbutanoate (**6**) can be isolated

Table 2. Effect of the nature of the sulfinate (reaction conditions: the reaction is carried out in DMF (120°C) with 1.5 equiv. of potassium carbonate)

Entry	Catalyst	Reaction time	Yield (%)[a]	Isolated yield (%)
1	None	21 h	54	52
2[b]	Sodium *p*-toluenesulfinate	7 h	76	64
3[b]	Sodium methanesulfinate	2 h	92	83

[a] GC yield, measure at the maximum conversion with biphenyl as internal standard.
[b] Reaction with 0.25 equiv. of sulfinate.

Table 3. Effect of the concentration of catalyst (reaction conditions: the reaction is carried out in DMF (120°C) with 1.5 equiv. of potassium carbonate)

Entry	Catalyst[a] (equiv.)	Reaction time	Yield (%)[b]	Isolated yield (%)
1	0	21 h	54	–
2	0.02	26 h	65	–
3	0.05	4 h	86	–
4	0.25	2 h	92	83
5	1.00	2 h	88	–

[a] Reaction with sodium methanesulfinate as catalyst.
[b] GC yield, measured at the maximum conversion with biphenyl as internal standard.

Table 4. Effect of the temperature

Entry	Temperature	Reaction time	Catalyst[a] (equiv.)	Yield (%)[b]
1[c]	80°C	22 h	0.25	96
2[c]	100°C	8 h	0.25	92
3[c]	100°C	8 h	0.10	95
4[c]	120°C	1 h	0.25	89

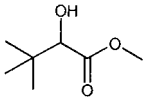
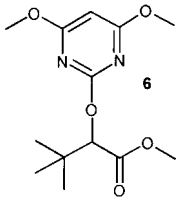
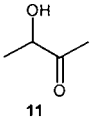
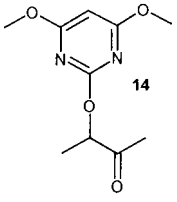
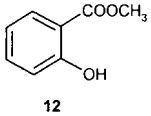
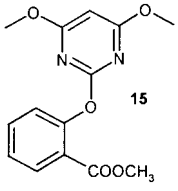
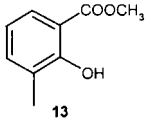
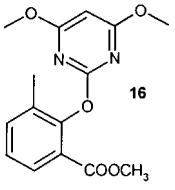
[a] Catalyst: sodium methanesulfinate.
[b] GC yield, measure at the maximum conversion with biphenyl as internal standard.
[c] Reaction conditions: the reaction is carried out in DMF with 1.5 equiv. of potassium carbonate.

Table 5. Effect of the nature of the base

Entry	Base	Reaction time	Yield (%)[a]
1[b]	Potassium carbonate	1 h	89
2[b]	Sodium carbonate	7 h	88
3[b]	Sodium acetate	8 h	11
4[b]	Diisopropylethylamine	6 h	14
5[c]	Sodium methanolate	0.5 h	51

[a] GC yield, measured at the maximum conversion with biphenyl as internal standard.
[b] Reaction conditions: the reaction is carried out in DMF (120°C) with 1.5 equiv. of base and 0.25 equiv. of catalyst.
[c] Reaction carried out without catalyst. The reaction conversion stopped after 0.5 h (large proportion of side reactions).

Table 6. Catalytic effect of sulfinate in the preparation of pyrimidinyloxy derivatives

Entry	Hydroxyderivative	Product	Without catalyst		With catalyst	
			Reaction conditions[a]	Yield (%)[b]	Reaction conditions[a]	Yield (%)[b]
1	 10	 6	120°C/21 h	52	120°C/2 h	83
2	 11	 14	120°C/23 h	46	120°C/3 h	80
3	 12	 15	120°C/5 h	69	120°C/1.5 h	77
4	 13	 16	120°C/24 h	55	120°C/8 h	66

[a] Reaction conditions: the reaction is carried out in DMF with 1.5 equiv. of potassium carbonate.
[b] Isolated yield.

in 83% yield after 2 h instead of 52% yield after 21 h in absence of sulfinate (Entry 1).

The influence of the concentration of sodium methanesulfinate has been investigated (Table 3). With 2% of sulfinate (Entry 3) relative to 2-chloro-4,6-dimethoxypyrimidine (**5**), the catalytic effect is very small. Above 25% of sulfinate, there is practically no more gain of reactivity. The optimal conditions for the reaction are obtained with 5–10% of sodium methanesulfinate relative to **5**.

The higher yields were obtained for reactions carried out at 80°C, with 96% conversion after 22 h (Table 4, Entry 1). Logically, increasing of the temperature has a direct influence on the reaction rate, but, as previously mentioned, the stability of the product is affected by higher temperature. Thus, at 120°C, a maximum conversion of 89% was obtained after 1 h (Entry 4).

Different bases (mineral and organic) have been tested (Table 5). The best reaction conditions were obtained in presence of potassium carbonate (Entry 1). Sodium carbonate is less reactive (Entry 2).

Application examples

By applying the developed method, some pyrimidinyloxy derivatives have been synthesised from 2-chloro-4,6-dimethoxypyrimidine (**5**) (Table 6). In all cases the reactivity of the substitution reaction could be clearly increased by using sodium methanesulfinate (0.25 equiv.).

In conclusion, we have developed an easy method to enhance the rate of substitution as well as the yield in the reaction of 2-chloro-4,6-dimethoxypyrimidine (**5**) with alkoxy or aryloxy nucleophiles, using sodium methanesulfinate as catalyst.

Experimental

All starting materials and solvents were reagent grade and used as received. Melting points were determined on a Büchi 535 apparatus and were not corrected. ^{1}H NMR (400 MHz) spectra were recorded on a VARIAN spectrometer. Chemical shifts are reported as parts per million. Tetramethylsilane was used as internal standard. Coupling constants *J* are given in Hertz.

Preparation of reactants and intermediates

2-Chloro-4,6-dimethoxypyrimidine (5). It was prepared according to the patent procedure.[11]

2-Hydroxy-3,3-dimethylbutanoic acid. It was prepared according to the literature procedure.[15]

Methyl 2-hydroxy-3,3-dimethylbutanoate (10). A stirred mixture of 2-hydroxy-3,3-dimethylbutanoic acid (50.0 g; 365 mmol), acetyl chloride (2.9 g; 37 mmol) in methanol (90 mL) was heated to reflux (~70°C) for 4 h. The reaction mixture was then concentrated under vacuum and the residue was diluted with ethyl acetate (300 mL). The organic solution was washed with a saturated aqueous solution of sodium hydrogencarbonate (3×140 mL) and dried over magnesium sulfate. After evaporation of the solvent, 39.1 g (69%) of an orange oil (GC analysis: 94% area) was obtained. ^{1}H NMR (d_6-DMSO): δ 5.27 (1H, d, J=6.0 Hz); 3.69 (1H, d, J=6.0 Hz); 3.62 (3H, s); 0.88 (9H, s).

4,6-Dimethoxy-2-(toluene-4-sulfonyl)pyrimidine (7b). Under argon, a well stirred suspension of 2-chloro-4,6-dimethoxypyrimidine (**5**) (4.38 g; 25.0 mmol), sodium *p*-toluenesulfinate (4.68 g; 26.3 mmol), potassium carbonate (5.17 g; 37.5 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated to 100°C for 5 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (60°C/20 mm Hg) and the residue partitioned between water (30 mL) and dichloromethane (30 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic phase was washed with water (15 mL), dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 3.79 g (51% [80% conversion]) of a white powder; mp 129.2–133.4°C. ^{1}H NMR (d_6-DMSO): δ 7.92 (2H, d, J=8.4); 7.50 (2H, d); 6.48 (1H, s); 3.87 (6H, s); 2.43 (3H, s); GC/MS (*m*/*e*): 294 (M^+); 279; 261; 209.

4,6-Dimethoxy-2-(methylsulfonyl)pyrimidine (7a). It can be prepared by oxydation of the methylthio-pyrimidine **8** according to the literature procedure[9] or by reaction of the 2-chloropyrimidine **5** with sodium methanesulfinate with the above procedure (**7b**).

Methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-dimethylbutanoate (6)

Preparation from 4,6-dimethoxy-2-(toluene-4-sulfonyl)-pyrimidine (7b). Under argon, a well stirred suspension of 4,6-dimethoxy-2-(toluene-4-sulfonyl)pyrimidine (**7b**) (2.94 g; 10.0 mmol), methyl 2-hydroxy-3,3-dimethylbutanoate (**10**) (1.55 g [94%]; 10.0 mmol), and potassium carbonate (2.07 g; 15.0 mmol) in *N*,*N*-dimethylformamide (20 mL) was heated to 100°C for 5 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (60°C/20 mm Hg) and the residue partitioned between water (30 mL) and ethyl acetate (30 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (30 mL). The combined organic phase was washed with water (15 mL), dried over magnesium sulfate and concentrated. The desired product crystallised and was dried under vacuum giving 2.30 g (80.9%) of slightly yellow crystals (GC analysis: 99 area %).

Preparation from 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (7a). Under argon, a well stirred suspension of 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (**7a**) (2.18 g; 10.0 mmol), methyl 2-hydroxy-3,3-dimethylbutanoate (**10**) (1.62 g [94%]; 10.5 mmol), and potassium carbonate (2.07 g; 15.0 mmol) in *N*,*N*-dimethylformamide (20 mL) was heated to 60°C for 3 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (60°C/20 mm Hg) and the residue partitioned

between water (40 mL) and ethyl acetate (40 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (40 mL). The combined organic phase was washed with water (20 mL), dried over magnesium sulfate and concentrated. The desired product crystallised and was dried under vacuum giving 2.76 g (93.8%) of slightly yellow crystals (GC analysis: 97% area).

Preparation from 2-chloro-4,6-dimethoxy-pyrimidine (5). Under argon, a well stirred suspension of 2-chloro-4,6-dimethoxypyrimidine (**5**) (4.38 g; 25.0 mmol), methyl 2-hydroxy-3,3-dimethylbutanoate (**10**) (3.90 g [94%] 25.0 mmol), sodium methanesulfinate (0.66 g; 6.3 mmol) and potassium carbonate (5.17 g; 37.5 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated to 120°C for 3 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (70°C/20 mm Hg) and the residue partitioned between water (30 mL) and dichloromethane (30 mL). The organic phase was separated and the aqueous phase extracted with dichloromethane (20 mL). The combined organic phase was washed with water (15 mL), dried over magnesium sulfate and concentrated. The desired product crystallised and was dried under vacuum giving 5.93 g (82.7%) of slightly yellow crystals (GC analysis: 99 area %); mp 104.4–107.0°C. ^{1}H NMR (d_6-DMSO): δ 5.88 (1H, s); 4.70 (1H, s); 3.85 (6H, s); 3.65 (3H, s); 1.07 (9H, s). GC/MS (*m*/*e*): 284 (M^+); 269; 228; 196; 169; 157.

Preparation of pyrimidinyloxy derivatives by catalysis with sodium methanesulfinate.

3-(4,6-Dimethoxypyrimidin-2-yloxy)-3,3-butan-2-one (14). Under argon, a well stirred suspension of 2-chloro-4,6-dimethoxypyrimidine (**5**) (4.38 g; 25.0 mmol), 3-hydroxy-2-oxobutane (**11**) (2.31 g; 26.2 mmol), sodium methanesulfinate (0.66 g; 6.3 mmol) and potassium carbonate (5.17 g; 37.5 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated to 120°C for 3 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (70°C/20 mm Hg) and the product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 4.58 g (80.4%) of a slightly yellow oil (GC analysis: 99% area). ^{1}H NMR (d_6-DMSO): δ 5.87 (1H, s); 5.20 (1H, q, J=7.1 Hz); 3.81 (6H, s); 2.15 (3H, s); 1.43 (3H, d, J=7.1 Hz). GC/MS (*m*/*e*): 226 (M^+); 211; 183; 157; 139.

Methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoate (15). Under argon, a well stirred suspension of 2-chloro-4,6-dimethoxypyrimidine (**5**) (4.38 g; 25.0 mmol), methyl 2-hydroxybenzoate (**12**) (3.80 g; 25.0 mmol), sodium methanesulfinate (0.66 g; 6.3 mmol) and potassium carbonate (5.17 g; 37.5 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated to 120°C for 1.5 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (70°C/20 mm Hg) and the residue partitioned between water (30 mL) and dichloromethane (30 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic phase was washed with water (15 mL), dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 5.76 g (77.0%) of a slightly yellow solid (GC analysis: 97% area); mp 106.7–108.3°C. ^{1}H NMR (d_6-DMSO): δ 7.91 (1H, dd, J=7.9 Hz, 1.6); 7.69 (1H, dt, J=7.9, 1.6 Hz); 7.41 (1H, dt, J=7.6, 1.3 Hz); 7.33 (1H, dd, J=8.1, 1.1 Hz); 5.95 (1H, s); 3.74 (6H, s); 3.62 (3H, s); GC/MS (*m*/*e*): 290 (M^+); 231.

Methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-3-methylbenzoate (16). Under argon, a well stirred suspension of 2-chloro-4,6-dimethoxypyrimidine (**5**) (4.38 g; 25.0 mmol), methyl 2-hydroxy-3-methylbenzoate (**13**) (4.17 g; 25.0 mmol), sodium methanesulfinate (0.66 g; 6.3 mmol) and potassium carbonate (5.17 g; 37.5 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated to 120°C for 8 h (the conversion was followed by TLC). The reaction mixture was then concentrated under vacuum (70°C/20 mm Hg) and the residue partitioned between water (30 mL) and dichloromethane (30 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic phase was washed with water (15 mL), dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 5.23 g (65.8%) of a slightly yellow solid (GC analysis: 96% area); mp 73.8–79.1°C. ^{1}H NMR (d_6-DMSO): δ 7.74 (1H, dd, J=7.6, 1.7 Hz); 7.58 (1H, dd, J=7.4, 1.6 Hz); 7.30 (1H, t, J=7.6 Hz); 5.95 (1H, s); 3.74 (6H, s); 3.62 (3H, s); 2.17 (3H, s); GC/MS (*m*/*e*): 304 (M^+); 273; 245.

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