Pergamon

Tetrahedron 55 (1999) 405–412

TETRAHEDRON

Carbonylation of 2-Chloro-4,6-dimethoxypyrimidine and 2-(Chloromethyl)-4,6-dimethoxypyrimidine

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Received 29 May 1998; revised 17 August 1998; accepted 18 August 1998

Abstract: The preparation of pyrimidine-2-carboxylates and 2-pyrimidineacetates by alkoxycarbonylation of respectively 2-chloropyrimidine and 2-(chloromethyl)pyrimidine with carbon monoxide in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene is described. The new process uses readily available starting materials and affords the corresponding esters in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Carbonylation reactions; Carboxylic acid esters; Heck type reactions; Pyrimidines.

Introduction

A Carbonylation of 2-Chloro-4,6-dimethoxypyrimidine

4,6-Dimethoxypyrimidines bearing a carboxylic acid function at the 2-position (**2**) are important intermediates for the preparation of antihypertensive and antithrombotic drugs [1] as well as herbicides and plant growth regulators [2,3] or fungicides [4]. Thus, 4,6-dimethoxypyrimidine-2-carboxylic acid (**2**, R=H) has been used for the preparation of numerous sulfonamide herbicides such as **3** [2] (Figure 1).

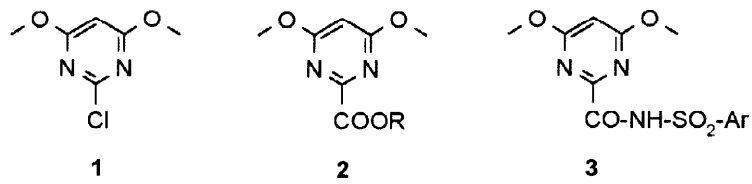


Figure 1. **Pyrimidine sulfonamides (3) from pyrimidine-2-carboxylates (2).**

Preparation of **2** often involves either tedious procedures or the use of expensive [5] or toxic reagents [6]. Pyrimidine-2-carboxylates have also been prepared by oxidation of 2-methylpyrimidines, using selenium dioxide [7] or potassium permanganate [8]. These methods usually afford low yields, thus, an alternative procedure is desirable. Based on our experience in the carbonylation of chloroheterocycles [9-12], we thought to use this

PII: S0040-4020(98)01038-2

methodology for the preparation of pyrimidine-2-carboxylates by alkoxycarbonylation of 2-chloro-4,6-dimethoxypyrimidine (**1**).

B Carbonylation of 2-(Chloromethyl)-4,6-dimethoxypyrimidine

Several examples of the use of 4,6-dimethoxy-2-pyrimidineacetic acid (**5**, R=H) for the preparation of pyrimidinesulfonamides such as **6** are described in the patent literature. These substances constitue a new class of herbicides and plant growth regulators [2,13-14] (Figure 2).

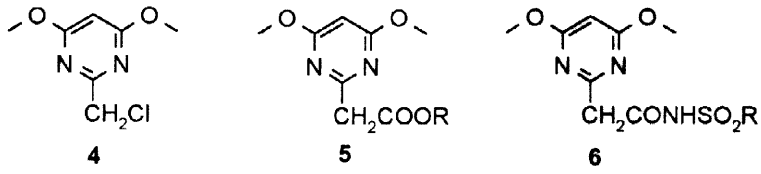
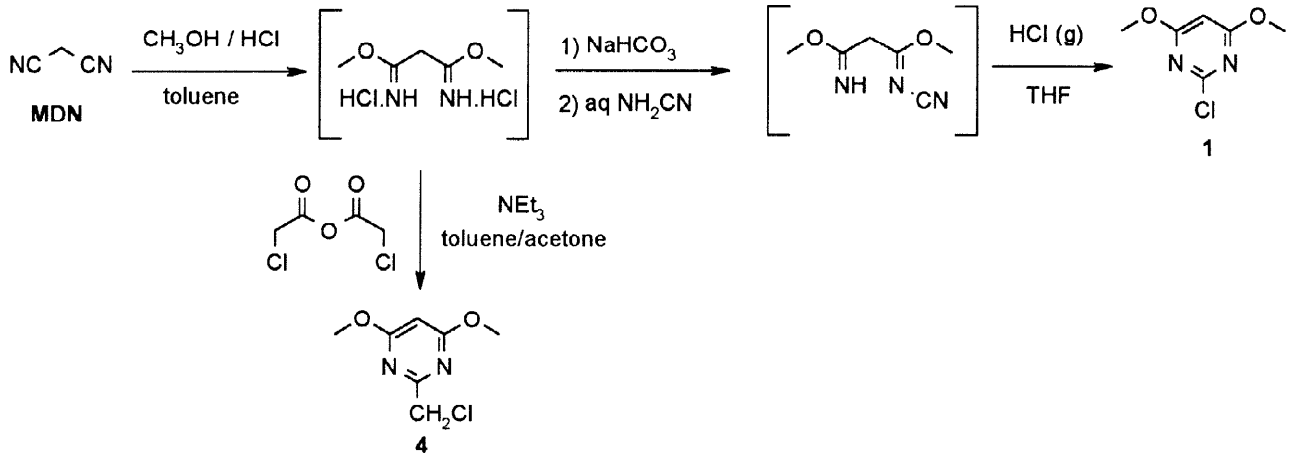


Figure 2. **Pyrimidinesulfonamides (6) from 2-pyrimidineacetates (5).**

No direct and efficient method is currently available for the preparation of 4,6-dimethoxy-2-pyrimidineacetic acid derivatives (**5**). For example [5], the classical synthesis of **4** via cyanation, followed by alcoholysis affords the methylester of 4,6-dimethoxy-2-pyrimidineacetic acid (**5**, R=CH_3) in relatively low yield (below 40%). 2-Pyrimidineacetates have also been prepared in low yield by cyclocondensation reactions [15].

Our success in the carbonylation of chloroheterocycles [9-12], prompted us to extend this concept to the preparation of 2-pyrimidineacetates by alkoxycarbonylation of 2-(chloromethyl)-4,6-dimethoxypyrimidine (**4**).

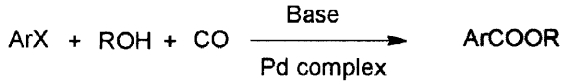
Both, 2-chloro-4,6-dimethoxypyrimidine (**1**) [16] and 2-(chloromethyl)-4,6-dimethoxypyrimidine (**4**) [17] are readily available, in good yields, from malonodinitrile (MDN) (Scheme 1).



Scheme 1. **Preparation of 2-chloro-4,6-dimethoxypyrimidine (1) and 2-(chloromethyl)-4,6-dimethoxypyrimidine (4) from MDN.**

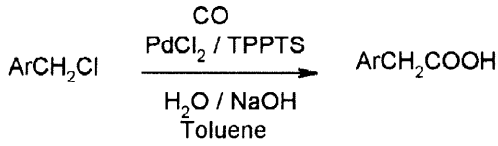
Results and Discussion

The carbonylation [18] of arylhalides (Scheme 2) in presence of nucleophiles such as H_2O, ROH, RNH_2 or carboxylate salts affords carboxylic acids, esters, amides or mixed anhydrides, respectively. In general, these transformations give good results with aryl bromides or iodides using palladium catalysts as described by Heck and co-workers[1].



Scheme 2. **Carbonylation of arylhalides.**

Similarly the transition metal-catalyzed carbonylation of benzylic compounds is a valuable tool for the synthesis of carboxylic acid derivatives. Catalysts used for this type of transformation are Ni, Co, Rh, Pt, Fe, but mostly Pd catalysts are used for reasons of activity and selectivity. Unlike aryl halides, benzylic halides are susceptible to nucleophilic attack and elimination reactions. A major drawback for most carbonylations of benzylic halides[2] thus far has been the large amount of catalyst (1 - 20 mol%) and phase transfer reagents (5 - 10 mol%) needed for high conversion and yields. A new approach [19,20] using water-soluble Pd catalysts with TPPTS (sodium tris-sulfonatophenylphosphine) as a ligand offers more efficient product isolation as well as being a more active catalyst system (Scheme 3). Only one example of a carbonylation of a heterocycle at the benzylic position [21] has been found in the literature and it concerned the carbonylation of a heterobenzyl mesylate[3].



Scheme 3. **Carbonylation reaction at the benzylic position.**

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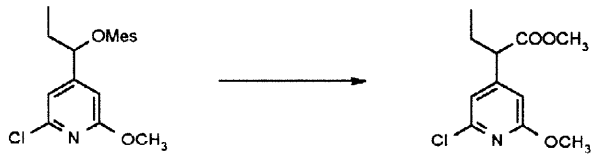
[1] Typical reaction conditions (Heck): 100-150°C and 1-3 atm of carbon monoxide in the presence of 1-2% of $Pd(PPh_3)_2Cl_2$, using the reactant alcohol as solvent and a tertiary amine as the acid acceptor.

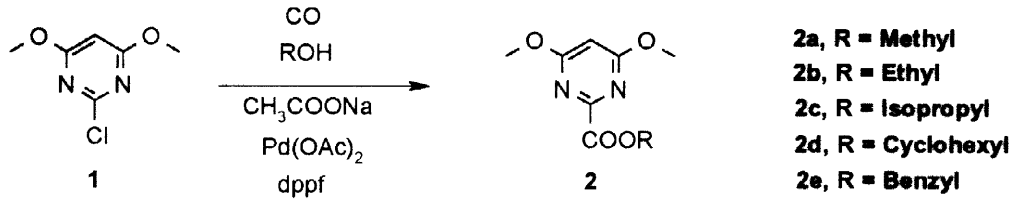
[2] Though the carbonylation of the benzylic alcohols is known to proceed well, we were limited by the availability of the 2-hydroxymethylpyrimidine.

[3] The alkoxycarbonylation outlined below was achieved in 85% yield from a heterobenzyl mesylate. The reaction was carried out with carbon monoxide (10 bar) in the presence of 2 equiv. of triethylamine in methanol and 2.0 mol % of dichlorobis(triphenylphosphine)palladium at 60°C for 10h.



A Carbonylation of 2-Chloro-4,6-dimethoxypyrimidine

We report here for the first time the carbonylation of 2-chloro-4,6-dimethoxypyrimidine (**1**) for the preparation of pyrimidine-2-carboxylates. Esters of 4,6-dimethoxypyrimidine-2-carboxylates (**2**) (Scheme 4) were obtained by alkoxycarbonylation of **1** with carbon monoxide at 15 bar in the presence of sodium acetate as acid acceptor, a catalytic amount of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) as ligand.



Scheme 4. **Alkoxycarbonylation of 2-chloro-4,6-dimethoxypyrimidine.**

All esters (**2a - 2e**) were prepared in good to excellent yield using the reaction conditions outlined below (Table 1).

Table 1. **Preparation of esters from 2-chloro-4,6-dimethoxypyrimidine.**

Entry	Solvent	Reaction conditions[a]	Esters[b] [%]
1	Methanol	165°C/2h	**2a** : 90
2	Ethanol	160°C/2.5h	**2b** : 87
3	Isopropanol	170°C/4h	**2c** : 54
4	Cyclohexanol	160°C/3h	**2d** : 75
5	THF/Benzyl alcohol (2 equiv.)	160°C/3h	**2e** : 76

[a] Reaction conditions : 3 mol% of ligand (dppf) and 0.2 mol% of catalyst (palladium acetate); 15 bar CO.
[b] Isolated yield after flash chromatography.

Initially, the reactions were carried out in tetrahydrofuran with 2 to 4 equivalents of the corresponding alcohol (Entries 1-2; Table 2). However volatile alcohols are more conveniently used as solvents because it greatly simplifies the work up and also provide higher yields (Entry 5). Among the ligands tested - 1,4-bis(diphenylphosphino)butane, triphenylphosphine, tris(4-methoxyphenyl)phosphine and 1,1'-bis(diphenylphosphino)ferrocene (dppf) - the last one gave the best results (Entry 5). Indeed, dppf gave a complete conversion in a shorter reaction time under slightly milder reaction conditions. With the other ligands, complete conversion could also be achieved, but only under more forcing conditions which were detrimental to the isolated yield, probably due to either hydrolysis or decarboxylation of the ester. The combination of dichlorobis(triphenylphosphine)palladium and 1,4-bis(diphenylphosphino)butane (Entry 1) is often cited in the literature, but in our case, relatively vigorous reaction conditions were necessary to complete the conversion. Palladium acetate gave a better yield (Entry 2) although the conversion was lower.

Table 2. **Comparison of reaction conditions for the alkoxycarbonylation reaction.**

Entry	Solvent	Reaction conditions[a]	Ligand[b]	Catalyst[c]	Yield[d] [%]	Conversion[e] [%]
1	THF/Methanol (3 eq.)	180°C/6h	dppb	$PdCl_2(Ph_3P)_2$	**2a** : 71	99
2	THF/Methanol (3 eq.)	165°C/4h	dppf	$Pd(OAc)_2$	**2a** : 85	92
3	Methanol	170°C/4h	Ph_3P	$Pd(OAc)_2$	-	42
4	Methanol	170°C/4h	tmpp	$Pd(OAc)_2$	-	62
5	Methanol	165°C/2h	dppf	$Pd(OAc)_2$	**2a** : 90	100

[a] Reaction conditions : 3 mol% of ligand and 0.2 mol% of catalyst; 15 bar CO.

[b] Ligands : 1,4-bis(diphenylphosphino)butane (dppb); triphenylphosphine (Ph_3P); tris(4-methoxyphenyl)phosphine (tmpp) and 1,1'-bis(diphenylphosphino)ferrocene (dppf).

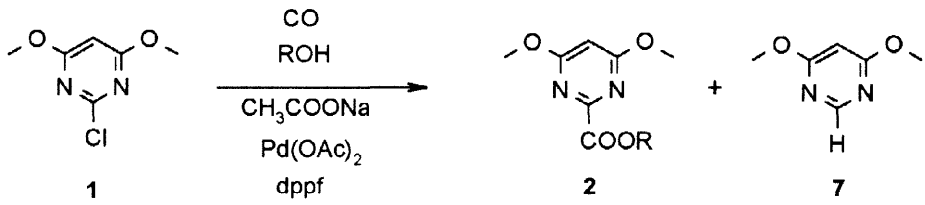
[c] Catalysts : dichlorobis(triphenylphosphine)palladium ($PdCl_2(Ph_3P)_2$) and palladium acetate ($Pd(OAc)_2$).

[d] Isolated yield after flash chromatography.

[e] Conversion : Except the product (**2**) and the starting material (**1**) no other products were detected by GC analysis of the crude reaction mixture.

Preliminary attempts showed that the optimal carbon monoxide pressure (Table 3) was in the range of 12 - 20 bar (initial pressure). When the reactions were carried out at lower pressure (< 9 bar) (Entries 1 and 2), we not only observed a lower conversion but also an increasing proportion of 4,6-dimethoxypyrimidine (**7**) (up to 18%) formed by reduction[1] of 2-chloro-4,6-dimethoxypyrimidine (**1**) (Scheme 5). Up to 9 bar of pressure (Entries 3 - 5), the conversion to **2b** was complete and no side-products could be detected in the reaction mixture.

Scheme 5. **Formation of 4,6-dimethoxypyrimidine at low carbon monoxide pressure.**



1 **2** **7**

[1] The probable origin of the reduction reaction has been examined in the preceding article of this journal.

Table 3. **Effect of the carbon monoxide pressure.**

Entry	Initial pressure[a] [bar]	Final pressure [bar]	1 [%]	2b [%]	7 [%]	2b, Yield[b] [%]
1	1.5	1.0	62	18	18	8
2	5.7	1.3	27	66	6	57
3	9.0	2.5	<1	97	2	87
4	12.0	7.0	-	100	-	93
5	19.0	12.5	-	100	-	93

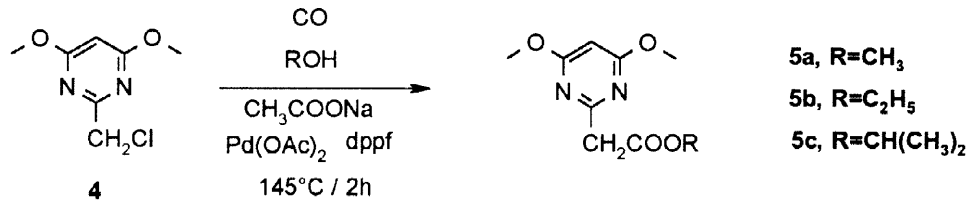
GC analysis of the crude reaction mixture.

[a] Reaction conditions : 3 mol% of ligand (dppf) and 0.2 mol% of catalyst (palladium acetate); sodium acetate (3 equiv); in ethanol 150°C/3h.

[b] Isolated yield after flash chromatography.

B Carbonylation of 2-(Chloromethyl)-4,6-dimethoxypyrimidine

We describe hereafter (Scheme 6) the carbonylation of 2-(chloromethyl)-4,6-dimethoxypyrimidine (**4**), a new practical synthesis of 4,6-dimethoxy-2-pyrimidineacetates (**5**). The alkoxycarbonylation of **4** was carried out with carbon monoxide (15 bar) in the presence of sodium acetate as acid acceptor, an alcohol as solvent and reagent, 0.2 mol% of palladium acetate and 3.0 mol% of 1,1'-bis(diphenylphosphino)ferrocene (dppf) as ligand at 145°C for 2h. Even with a low concentration of catalyst and relatively mild reaction conditions, good yields could be obtained. Thus, the methyl ester (**5a**), the ethyl ester (**5b**), the isopropyl ester (**5c**) were prepared with 59%, 82% and 54% yield (respectively, after chromatography).



Scheme 6 **Alkoxycarbonylation of 2-(chloromethyl)pyrimidine with carbon monoxide.**

Conclusion

Compared to other traditional methods, this carbonylation methodology provides a simple and expedient access to a variety of 4,6-dimethoxypyrimidine-2-carboxylic acid derivatives (**2**) and 4,6-dimethoxy-2-pyrimidineacetic acid derivatives (**5**), using readily available 2-chloro-4,6-dimethoxypyrimidine (**1**) or respectively 2-(chloromethyl)-4,6-dimethoxypyrimidine (**4**).

Experimental

Reagents and solvents were reagent grade and were used as received. Melting points were determined on a Büchi 535 apparatus and have not been 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.

Alkoxycarbonylation. General Procedure. The reactions were carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order : (1) alcohol (40 mL) (or 40 mmol of alcohol and 40 mL of tetrahydrofuran), (2) sodium acetate (1.92 g, 60 mmol), (3) chloropyrimidine or 2-(chloromethyl)pyrimidine (20 mmol), (4) 1,1'-bis(diphenylphosphino)-ferrocene (333 mg, 0.6 mmol [3%mol]) and (5) palladium acetate (9.0 mg, 0.04 mmol [0.2%mol]. The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 bar. The reaction mixture was then heated to the desired temperature [160°C to 180°C] with rapid stirring. After completion the reaction mixture was cooled to room temperature and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:1).

A Carbonylation of 2-Chloro-4,6-dimethoxypyrimidine

Methyl 4,6-dimethoxypyrimidine-2-carboxylate (2a). Yield 90%; mp 129.7 - 131.1 °C. ^{1}H NMR ($CDCl_3$): δ 6.16 (1 H, s); 4.03 (6 H, s); 3.99 (3 H, s). GC/MS (m/e) : 198 (M^+); 197; 183; 168; 139; 125; 108; 93.

Ethyl 4,6-dimethoxypyrimidine-2-carboxylate (2b). Yield 87%; mp 55.9 - 57.4 °C. ^{1}H NMR ($CDCl_3$): δ 6.15 (1 H, s); 4.46 (2 H, q, J = 7.1); 4.02 (6 H, s); 1.43 (3 H, t, J = 7.1). GC/MS (m/e) : 213; 212 (M^+); 211; 183; 154; 140; 125.

Isopropyl 4,6-dimethoxypyrimidine-2-carboxylate (2c). Yield 54%; mp 64.6 - 66.6 °C. ^{1}H NMR ($CDCl_3$): δ 6.14 (1 H, s); 5.29 (1 H, hept, J = 6.3); 4.02 (6 H, s); 1.42 (6 H, d, J = 6.3). GC/MS (m/e) : 226 (M^+); 211; 183; 167; 140.

Cyclohexyl 4,6-dimethoxypyrimidine-2-carboxylate (2d). Yield 75%; mp 99.0 - 101.2 °C. ^{1}H NMR ($CDCl_3$): δ 6.13 (1 H, s); 5.06 (1 H, m); 4.02 (6 H, s); 2.0 (2 H, m); 1.8 (2 H, m); 1.6 (3 H, m); 1.4 (3 H, m). GC/MS (m/e) : 266 (M^+); 221; 185; 167; 139.

Benzyl 4,6-dimethoxypyrimidine-2-carboxylate (2e). The reaction is carried out in tetrahydrofuran (40 mL) with 40 mmol (4.33 g) of benzylalcohol. T(160 °C; bath); t(3h). Yield 76%; mp 96.8 - 98.1 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (2 H, d); 7.35 (3 H, m); 6.15 (1 H, s); 5.43 (2 H, s); 4.01 (6 H, s). GC/MS (m/e) : 275; 274 (M^+); 246; 168; 140.

4,6-Dimethoxypyrimidine (7). Isolated by-product. ^{1}H NMR ($CDCl_3$): δ 5.70 (1 H, s); 3.95 (1 H, s); 3.92 (6 H, s). GC/MS (m/e) : 140 (M^+); 139; 110; 98; 83; 68.

B Carbonylation of 2-(Chloromethyl)-4,6-dimethoxypyrimidine

Methyl (4,6-dimethoxypyrimidin-2-yl)acetate (5a). Yield 59%; yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.92 (1 H, s); 3.91 (6 H, s); 3.82 (2 H, s); 3.74 (3 H, s). GC/MS (m/e) : 212 (M^+); 211; 183; 169; 140.

Ethyl (4,6-dimethoxypyrimidin-2-yl)acetate (5b). Yield 82%; yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.91 (1 H, s); 4.22 (2 H, q, J = 7.1); 3.91 (6 H, s); 3.80 (2 H, s); 1.28 (3 H, t, J = 7.1). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3); 45.4

(CH_2); 54.0 (2x OCH_3); 60.9 (OCH_2); 87.9 (CH); 163.7(CO); 169.7 (CNN); 171.6 (2x CON). GC/MS (m/e) : 226 (M^+); 225; 211; 196; 181; 153; 122.

Isopropyl (4,6-dimethoxypyrimidin-2-yl)acetate (5c). Yield 54%; yellow oil. ^1H NMR ($CDCl_3$): δ 5.92 (1 H, s); 5.10 (1 H, hept, J = 6.3), 3.91 (6 H, s); 3.78 (2 H, s); 1.26 (6 H, d, J = 6.3). ^{13}C NMR ($CDCl_3$): δ 21.8 (2xCH_3); 45.6 (CH_2); 54.0 (2x OCH_3); 68.3 (CH); 87.9 (=CH); 163.9(CO); 169.2 (CNN); 171.6 (2x CON). GC/MS (m/e) : 240 (M^+); 239; 225; 197; 181; 154; 125; 113.

Acknowledgment

The authors would like to thank their colleagues in the Chemical Research and Development department for their support and especially Dr. Jean Paul Roduit and Dr. Andy Naughton for their valuable advice during the redaction of this manuscript.

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