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Microwave-assisted, facile, rapid and solvent-free one pot twocomponent synthesis of some special acylals



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ABSTRACT

A facile, rapid and solvent-free method for the conversion of acids and dihalomethane to the corresponding methylene diesters (acylals) using microwave as activators or assistor, is reported. This method is particularly powerful for the diesterification of carboxylic acids, which afford methylene diesters in good to excellent yields (up to >99%). When the intermediate is trapped, a "double successive S_N2 reactions" mechanism is proved.

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1. Introduction

Acylals have the general structure R_1 –CH(OOCR₂)₂, which were introduced by Hurd and Cantor [1]. They are important starting materials in organic synthesis, particularly for the synthesis of dienes and chiral allylic esters. They also act as cross-linking reagents for cellulose in cotton [2]. In spite of the fact that the first acylal was synthesized more than 150 years ago and a number of methods have been developed since then for this purpose, two synthetic routes predominate [3]. The most widely used route is the reaction of aldehydes with carboxylic anhydrides in the presence of an acid catalyst such as protic or Lewis acid, iodine, and Nbromosuccinimide [4]. Several inorganic heterogeneous reagents have also been developed such as sulfated zirconia, montmorillonite clay, expansive graphite, and zeolite HSZ-360 [5]. Wicke and Engelhardt developed the second major route by the reaction of silver carboxylates with 1.1-dihaloalkanes. When cations other than silver ions were used as the carboxylate counterion, the reaction conditions were slightly modified [6].

Thus, although acylals are readily available, the existing methodologies suffer from one or more of the following disadvantages [7]: longer reaction time, low yields, the use of

harmful solvents, the use of sensitive and costly catalysts and the requirement of special apparatus.

Recently, we developed a novel method for the conversion of acids and dihalomethane to the corresponding methylene diesters (acylals). Our method overcomes the abovementioned disadvantages that make this method attractive for large-scale synthesis. Surprisingly, dichloromethane, which is a relatively inert compound, seldom acts as a strong enough electrophile to react with carboxylic acids [8]. The formation of methylene diester (**1a**), as shown in Scheme 1, was unexpected.

2. Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers. ¹H NMR and ¹³C NMR spectra were acquired on 300 or 500 MHz Bruker Avance spectrometer [9] with CDCl₃ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts were reported in δ (ppm). Mass spectra (MS) data were obtained using an Esquire 6000 Mass Spectrometer. The single crystal X-ray diffraction data was collected at 293 K with graphite monochromated Mo-K α radiation (λ = 0.071073 nm), and a Rigaku SCX mini diffractometer with the ω -scan technique was used. The lattice parameters were integrated using vector analysis and refined from the diffraction matrix, and the absorption correction was carried out by using Bruker SADABS program with the multi-scan method [10]. CCDC reference numbers 978475 contains the

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Scheme 1. Discovery of methylene diester.

supplementary crystallographic data in CIF format reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_re-quest/cif. Column chromatography was performed with silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd., China).

3. Results and discussion

An impurity generated during the synthesis of Vinpocetine (API) aroused our attention. It is very interesting that the results of the reaction stirring in oil bath and microwave oven are very different. When the reaction was stirred in oil bath, the HPLC analyses showed that the content of impurity increased with increasing time. The reaction was continued for 7 days to obtain this impurity, and the yield of the impurity increased from 0.1% to 10%. But in the condition of microwave, it needs only 45 min to reach this result. Then, the impurity was purified by column chromatography and the structure was established by the MS, ¹H NMR, and ¹³C NMR spectral analyses. The main difference in the ¹H NMR spectrum of the impurity than that of Vinpocetine was the disappearance of the H-20 (δ 4.40, 2H) and H-21 (δ 1.37, 3H) signals. New signals appeared at δ 6.25 in the ¹H NMR spectrum and at δ 80.86 in the ¹³C NMR and DEPT (135) spectra of the impurity to confirmed the presence of a methylene $(-CH_2-)$ group. The ESI-MS analysis showed the mass of the impurity at m/z657 [M+H]⁺. Thus, the structure of the impurity was established as the methylene diester (**1a**), as shown in Scheme 1.

Although the abovementioned diesterification between the acid and CH_2Cl_2 seemed to be an unexpected result for the synthesis of methylene diesters. To prove our conjecture, benzoic acid was chosen to test and verify the reaction. Methylene dibenzoate (**2a**) was isolated by column chromatography, and the molecular structure was unambiguously confirmed by the X-ray crystallographic analysis (Fig. 1).

Various conditions were evaluated for optimizing the reaction conditions, and the results are shown in Table 1. Inorganic bases such as K_2CO_3 , CS_2CO_3 , and NaOH slightly affected the reaction in oil bath and microwave, because they could not be dissolved in CH_2Cl_2 . To our delight, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)



Fig. 1. Molecular structure of methylene dibenzoate.

or s-collidine improved the isolated yield to >90% in oil bath, and the reaction time significantly decreased. But it did not happen in the other reactions using the bases as *N*,*N*-diisopropylethylamine (DIPEA), 4-methylmorpholine, triethylamine. Surprisingly, in the condition of microwave, the reactions using the organic bases were improved which afford methylene diesters in good to excellent yields (up to >99%).

To demonstrate the general applicability of this method, various para-substituted benzoic acids were reacted under the optimized reaction conditions, e.g., -Me, -OMe, -F, and -NO₂. The results are summarized in Table 2. The electronic effects and the nature of the substituents on the aromatic ring strongly affected the yields under the optimized reaction conditions. p-Nitrobenzoic acid was proved to be inert at low temperature. Several attempts to improve the outcome of this reaction by adding different catalysts (CuCl, CuBr, Cul, AgNO₃, Pd($C_2H_3O_2$) were unsuccessful. When the temperature of the reaction was raised to 120 °C, the yield of the reaction improved. Assuming that C-Br bond would be more reactive than C-Cl bond in this reaciton, CH₂Br₂ was reacted instead of CH₂Cl₂; however, the reaction was not successful. When the temperature of the reaction was raised up to 120 °C, the yield of the reaction improved. Intrigued by this result, we tried to synthesize methylidyne triesters by reacting benzoic acid (10 mmol) in CHCl₃ (5 mL) and N-methyl-2-pyrrolidon (NMP) (10 mL) at 200 °C in a microwave reactor; a new spot was detected by TLC. However, it was difficult to isolate the product to confirm its structure.

Based on the above-mentioned results, various heterocyclic carboxylic acids were investigated. They afforded the corresponding products in excellent yields. The results are summarized in Table 3.

Table 1

Optimization studies.



Entry	Lewis base	Conditions ^a	Yield (%) ^b
1	K ₂ CO ₃	$5 imes 24h/40^\circ C$	<5
2	K ₂ CO ₃	Microwave/1 h/40 °C	12
3	Cs ₂ CO ₃	$5 imes 24h/40^\circ C$	<5
4	Cs ₂ CO ₃	Microwave/1 h/40 °C	13
5	NaOH	$5 imes 24h/40^\circ C$	<5
6	NaOH	Microwave/1 h/40 °C	15
7	DIPEA	40 h/40 °C	10
8	DIPEA	Microwave/45 min/80 °C	92
9	4-Methylmorpholine	40 h/40 °C	18
10	4-Methylmorpholine	Microwave/45 min/80 °C	94
11	Triethylamine	40 h/40 °C	15
12	Triethylamine	Microwave/45 min/80 °C	93
13	DBU	8 h/40 °C	92
14	DBU	Microwave/45 min/80 °C	99
15	s-Collidine	8 h/40 °C	93
16	s-Collidine	Microwave/45 min/80 °C	99

 $^{a}\,$ All the reactions were carried out under the following conditions: benzoic acid 10 mmol; CH_2Cl_2, 30 mL; base 30 mmol.

^b Yields of the isolated products.

Table 2

Effect of different functional groups.



Entry	R	Conditions ^a	Yield (%) ^b
2	Н	45 min/80 °C	93
3	CH ₃	45 min/80 °C	95
4	OCH ₃	45 min/80 °C	97
5	F	45 min/80 °C	91
6	NO_2	45 min/80 °C	<1
		CuCl/80 °C/1 h ^c	<1
		CuBr/80 °C/1 h ^d	<1
		CuI/80 °C/1 h ^e	<1
		DBU/DMF: $CH_2Cl_2 = 5:1/120 \circ C/1.5 h^f$	22
		$CH_2Br_{2/}80 \ ^{\circ}C/1 \ h^{ m g}$	<1

^a Unless otherwise noted, the reaction was carried out on a *para*-substituted benzoic acid 10 mmol, CH₂Cl₂ 30 mL, base 30 mmol.

^b Yield of the isolated products.

^c 10 mmol CuCl.

^d 10 mmol CuBr.

^e 10 mm el Cul

^e 10 mmol Cul.

^f DMF 50 mL, CH₂Cl₂ 10 mL.

^g The boiling point of CH₂Br₂ is 96 °C.

From the abovementioned results (Table 2, entries **2–6**; Table 3, entries **7–11**), methylene diesters were observed unambiguously; other intermediates were not detected by the HPLC analyses except for the reaction between *p*-nitrobenzoic acid and CH₂Cl₂. When *p*-nitrobenzoic acid was used as the starting material, an intermediate was trapped. The ¹H-NMR spectrum of this intermediate confirmed the structure as chloromethyl-4-nitrobenzoate (**6b**). This was the only case when substantial amounts of a chloromethyl ester was observed and ruled out the possibility of path 2 in Scheme 2. Thus, we propose that this direct esterification most probably proceed *via* a double successive S_N2 processes.

Table	e 3
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	Direct	synthesis	of	methylene	diesters
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^a All the reactions were carried out under the following conditions: microwave 80 °C; heterocyclic carboxylic acid 10 mmol; CH₂Cl₂, 30 mL; DBU, 30 mmol.
 ^b Yields of the isolated products.



Scheme 2. Possible mechanism for the synthesis of methylene diesters [11].



Scheme 3. Selective reaction between acid and C-I bond.



Scheme 4. Competitive reaction between furan-2-carboxylic acid and benzoic acid.

To prove our proposed mechanism, the first was to explain that the chloromethyl esters did not form in other reactions. Therefore, we designed two reactions: the first reaction is using *p*-nitrobenzoic acid and CH_2ICI , and the result is shown in Scheme 3. As expected, both *p*-nitrobenzoic and chloromethyl-4-nitrobenzoate did not have sufficient activity to continue.

The second reaction is using furan-2-carboxylic acid (20 mmol), benzoic acid (10 mmol) and CH_2Cl_2 (50 mL) as the starting materials. The result is shown in Scheme 4. Methylene dibenzoate was not detected by the HPLC analysis. Because furan-2-carboxylic acid is more reactive than benzoic acid, it first reacted with CH_2Cl_2 . Because the C–Cl bond in the intermediate was more activated than that in CH_2Cl_2 , it reacted with both the types of carboxylic acids without selectivity. This result verified the proposed double successive S_N2 processes.

4. Conclusions

In summary, we established a facile, rapid and solvent-free method for preparing methylene diesters in good to excellent yields. Our studies show that CH₂Cl₂ is not an excellent solvent under mild reaction conditions. It is very important for the process development of active pharmaceutical ingredients. In this work, a "double successive S_N2 reactions" mechanism is also proved.

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