

A NEW FACILE SYNTHESIS OF DIMETHYL 4-(2-(2,6-BIS(METHOXYCARBONYL)PYRIDIN-4-YL)VINYL) PYRIDINE-2,6-DICARBOXYLATE

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A new facile synthesis of pyridine dicarboxylic acid derivative, dimethyl 4-(2-(2,6-bis(methoxycarbonyl)pyridin-4-yl)viny)pyridine-2,6-dicarboxylate (DVDPA), from dimethyl 4-(chloromethyl)pyridine-2,6-dicarboxylate (CMDPA) in presence of nitrogen bases has been described. The influences of different base/CMDPA molar ratio and different nitrogen bases were also investigated. The result has shown that the yield could reach 81 % when triethylamine was used and the molar ratio of base/CMDPA was 2.4. The overall yield of title compound via the three-step synthesis starting from dimethyl 4-(hydroxymethyl)pyridine-2,6-dicarboxylate (HMDPA) was improved to 69 %.

Key words: dimethyl 4-(2-(2,6-bis(methoxycarbonyl)pyridin-4-yl)viny)pyridine-2,6-dicarboxylate; pyridine dicarboxylic acid derivative; nitrogen base

НОВА И ЕДНОСТАВНА СИНТЕЗА НА ДИМЕТИЛ 4-(2-(2,6-БИС(МЕТОКСИКАРБОНИЛ)ПИРИДИН-4-ИЛ)ВИНИЛ)ПИРИДИН-2,6-ДИКАРБОКСИЛАТ

Опишана е нова едноставна синтеза на дериват на пиридиндикарбоксилната киселина, диметил-4-(2-(2,6-бис(метоксикарбонил)пиридин-4-ил)винил)пиридин-2,6-дикарбоксилат (DVDPA), со користење на диметил 4-(хлорометил)пиридин-2,6-дикарбоксилат (CMDPA) во присуство на азотни бази. Освен тоа, проучувано е влијанието на различен молски однос база/CMDPA и различните азотни бази. Резултатите покажаа дека приносот може да достигне 81 % кога се користи триетиламин при молски однос база/CMDPA од 2,4. Вкупниот принос на соединението е подобрен до 69 % преку синтеза во три чекори поаѓајќи од диметил 4-(хидроксиметил)пиридин-2,6-дикарбоксилат (HMDPA).

Клучни зборови: диметил 4-(2-(2,6-бис(метоксикарбонил)пиридин-4-ил)винил)пиридин-2,6-дикарбоксилат; дериват на пиридиндикарбоксилна киселина; азотна база.

1. INTRODUCTION

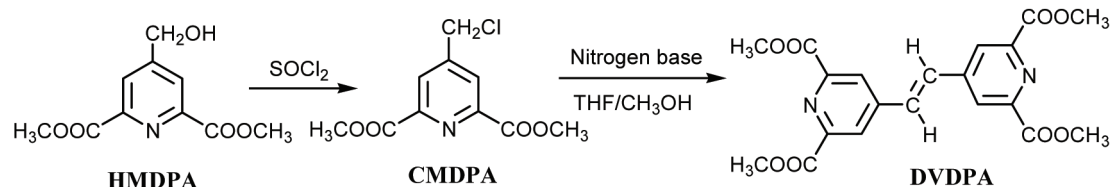
Our research group has recently been interested in synthesis of the pyridine dicarboxylic acid derivatives with rigid conjugated planar structure, which would be beneficial to the electronic negotiability [1], as many of them are useful in the field of fiber-optic telecommunications systems [2–5] and time-resolved fluoroimmunoassay (TR-FIA) [6, 7].

In recent years, increasing attention has been focused on organic reactions in aqueous media. Water is the most favorable solvent in terms of operating cost and environmental impact. The use of water as a solvent in organic synthesis is often surprisingly effective even for reactions that are traditionally carried out under anhydrous conditions. To the best of our knowledge the pyridine dicarboxylic acid derivative, DVDPA, has been reported only in our previous studies [8],

which was synthesized by a Wittig reaction of corresponding alkyltriphenylphosphonium salts with aromatic aldehydes in 52 % overall yield.

Herein we report the synthesis of DVDPA, which can be efficiently obtained from

dimethyl 4-(chloromethyl)pyridine-2,6-dicarboxylate (CMDPA) in substantially improved conditions by using nitrogen bases in aqueous solution in place of alkyltriphenylphosphonium salts with aromatic aldehydes (Scheme 1) [9].



Scheme 1

2. RESULTS AND DISCUSSION

The starting dimethyl 4-(chloromethyl)pyridine-2,6-dicarboxylate was prepared by the chlorination of dimethyl 4-(hydroxymethyl)pyridine-2,6-dicarboxylate (HMDPA) with sulfonyl dichloride (Scheme 1) [10]. The structure of CMDPA was confirmed by the spectra (MS, ^1H NMR) and elemental analysis. The ^1H NMR spectra revealed three characteristic singlets at 4.06, 4.45 and 8.27 ppm, assignable to CH_3 , CH_2 , and C_6H_2 , respectively. Its mass spectrum showed the molecular ion peak at m/z 243, which indicated that the prepared compound was indeed HMDPA.

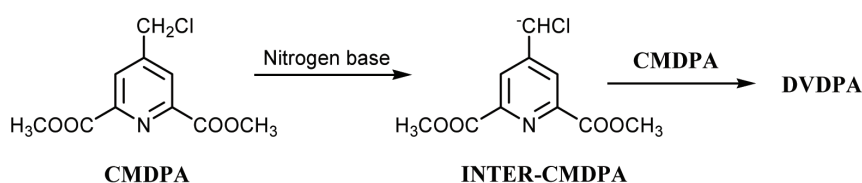
The influences of different nitrogen bases and the molar ratio of base/CMDPA on the product yield are shown in Table 1. When triethylamine was used and the molar ratio of triethylamine/CMDPA was 2.4, the product yield reached the maximum. The proposed mechanism is shown in Scheme 2. The key factor for obtaining high yields may be attributed to the controlled availability of hydroxide ion. The $\text{p}K_{\text{b}}$ values of the amines are in the correct range, to generate sufficient concentration of OH^- to deprotonate CMDPA and generate the anion INTER-CMDPA, and not to hydrolyze the esters present. Once the INTER-CMDPA is formed, it reacts with one molecule of CMDPA to

give the desired DVDPA. The suggested mechanism is similar to the one reported by Gilbert P. Sollott [9].

Table 1

DVDPA from Nitrogen Bases and CMDPA

Nitrogen base	Base/CMDPA molar ratio	DVDPA yield, %
Ammonia	1.6	58
	2.0	61
	2.4	65
	2.8	62
Dimethylamine	1.6	46
	2.0	51
	2.4	55
	2.8	51
Diethylamine	1.6	46
	2.0	51
	2.4	55
	2.8	51
Triethylamine	1.6	72
	2.0	74
	2.4	81
	2.8	76
Triethanolamine	1.6	5
	2.0	9
	2.4	12
	2.8	10



Scheme 2

In aqueous THF and methanol in the presence of nitrogen bases, starting from CMDPA, the pyridine dicarboxylic acid derivative, DVDPA, was obtained (Scheme 1). The mass spectra of the product revealed the molecular ion peak at the expected m/z 414. The elemental analysis data was consistent with the expected molecular formula. In the infrared spectra (see Experimental section) strong and sharp bands at 1000 cm^{-1} appear which are assignable to $\delta(\text{C}=\text{H})$, as well as the strong band at 1734 cm^{-1} assignable to the carbonyl group from the ester functional groups. The coupling constant obtained from the ^1H NMR spectrum of the proton ($\text{Py}-\text{CH}=\text{C}$) was 16 Hz, which confirmed that DVDPA had trans configuration of the double bond.

The new facile synthetic route is simpler, more cost-effective and more eco-friendly than the previously reported procedure [9], with an overall yield increase from 52 % to 69 %.

3. EXPERIMENTAL

Melting point was determined on a XR-4 apparatus and is uncorrected. IR spectra were recorded as KBr discs using an Avator-360-FT spectrum GX spectrophotometer. ^1H NMR spectra was recorded on a Bruker Advance RX300 analyzer in CDCl_3 with TMS as internal standard (400 Hz). Mass spectra were recorded on GC-MS HP-5988 (EI mode, fused-silica capillary column). Elemental analyses were recorded on a Perkin Elmer 2400 elemental analyzer. 4-(Hydroxymethyl)pyridine-2,6-dicarboxylate was synthesized according to the method by Ruiren Tang reported in the literature [11].

Dimethyl 4-(chloromethyl)pyridine-2,6-dicarboxylate (CMDPA): To a solution of HMDPA (6.0 g, 26.5 mmol) in anhydrous chloroform (50 mL), sulfur dichloride (4.8 g, 40.0 mmol) was added dropwise under nitrogen atmosphere at $-5\text{ }^\circ\text{C}$, then was stirred for about 40 min. The solvent was removed under reduced pressure and the crude product was purified by recrystallization from ethanol to give a 5.9 g (86 %) of

flaxen solid. mp $168\text{--}170\text{ }^\circ\text{C}$ (lit. [11] mp $168\text{--}170\text{ }^\circ\text{C}$). IR (KBr), ν/cm^{-1} : 3079, 2959, 2836, 1725, 1710, 1380, 1257, 1125, 798. EI-MS, (m/z , rel. intensity): 243 (M^+), 213 ($\text{M}-\text{OCH}_3$, 62 %), 184 ($\text{M}-\text{OCH}_3-\text{CO}$, 100 %). ^1H NMR (400 MHz, CDCl_3), δ : 8.27 (s, 2H, Py-H), 4.45 (s, 2H, CH_2Cl), 4.06 (s, 6H, OCH_3). EA (calculated/found for $\text{C}_9\text{H}_{10}\text{O}_5\text{N}$): % C 49.53 (49.18), H 4.17 (4.23), N 5.61 (5.37).

Dimethyl 4-(2-(2,6-bis(methoxycarbonyl)pyridin-4-yl)vinyl)pyridine-2,6-dicarboxylate (DVDPA): The reaction with triethylamine exemplify the general procedure which was used for all reactions summarized in Table 1. CMDPA (6.1 g, 25 mmol) was dissolved in THF (60 mL) and methanol (40 mL) and to this mixture a 6.0 g triethylamine dissolved in methanol (30 mL) and water (100 mL) was added. The mixture was stirred for 15 min, and then was heated to $50\text{ }^\circ\text{C}$ with stirring for 60 min. The reaction mixture was cooled to $10\text{ }^\circ\text{C}$, was allowed to stand for about 30 min, then it was filtered. The collected solid was recrystallised from methanol to give 4.2 g (81 %) of DVDPA as a whitish solid. mp $192\text{--}194\text{ }^\circ\text{C}$ (lit. [11] mp $191\text{--}193\text{ }^\circ\text{C}$). IR (KBr), ν/cm^{-1} : 3415, 2918, 1734, 1636, 1593, 1437, 1390, 1228, 1000, 911, 773, 696. ^1H NMR (CDCl_3), δ : 7.16-7.53 (d, 2H, $J=16.0\text{ Hz}$, $\text{Py}-\text{CH}=\text{C}$), 8.13 (s, 4H, Py-H), 4.04 (s, 6H, OCH_3). EA (calculated/found for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_8$): % C 57.36 (57.97), H 4.68 (4.35), N 6.32 (6.76).

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