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SHORT COMMUNICATION

A Microwave Step for the Synthesis of 4,5-Dicyanopyridazine: A Great Forerunner to Phthalocyanines

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Abstract:

4,5-Dicyanopyridazine (DCP) shows unexpected reactivity with dienophiles via Hetero Diels-Alder. Reactions involving this compound and alkynes or enamines was already described, and open possibilities to synthesize precursors for important macromolecules, like phthalonitriles used in phthalocyanines synthesis. Herein, we present a microwave synthetic step in the DCP synthetic route in order to minimize the time to synthesize this compound.

Keywords: 4,5-dicyanopyridazine; microwave; pyridazine; phthalonitriles

1. Introduction

DCP [1] shows an unexpected behavior in many unusual reactions for pyridazines. It might react with dienes, alkenes and cycloalkenes, with heterocyclic dienophiles like *N*-methylpyrrole and indole derivatives, with alkynes, enamines and other compounds.

Cecchi and co-workers [2] investigated the behavior of DCP in nucleophilic aromatic substitutions in pyrrole and indole systems in 2006. They synthetize a series of compounds that show that DCP react in formal SNAr2 process, not only a heterocyclic azadiene in inverse electron-demand Hetero Diels-Alder reactions.

Alfini and co-workers [3] elaborated a synthetic route using DCP as starting material to synthetize a series of aminocyanopyridazines through SNAr2 reactions with some significant yields, where DCP suffer a substitution of a CN group. These new materials open a way to another synthetic elaboration. Kobayashi, Nonomura and Nakai [4] used DCP as precursor to synthetize new precursors of a seven-membered carbon-ring-fused phthalocyanine analogues. This study showed that many types of precursor of phthalocyanines might be synthetized from the DCP.

The synthesis of DCP (**1**) and its potential uses was described elsewhere [1, 5-8]. Di Stefano and Castle synthetize DCP for first time in 1968 [7] from the pyridazine-4,5-dicarboxylic acid to dimethylpyridazine-4,5-dicarboxylate and subsequent dehydration of pyridazine-4,5-dicarboxamide (**2**). However, in 1985, Heinisch and Lötsch [9] (Letter b, Scheme 1) developed a facile preparation of diethyl pyridazine-4,5-dicarboxylate (**3**) from commercial and unsubstituted pyridazine (**4**).

In our work (Letter c, Scheme 1), the synthetic route was changed in some parameters in order to achieve better results in reaction time and yield. The main change was the use of microwave in the third step of classical route, that uses $POCl_3$ in reflux for 7-8 hours. Scheme 1 represents the synthetic route.

Better results in the third step were obtained in 20 minutes using microwave irradiations compared with 7-8 hours of $POCl_3$ reflux. Being so, the use of DCP can be encouraged to many applications including synthesis of substituted

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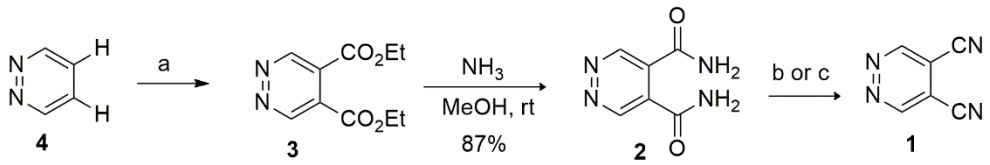
phthalocyanines with the most diverse ligands.



a: 30% aq. H_2O_2, ethyl pyruvate, -10 ºC, 15 min, so added pyridazine, $FeSO_4.H_2SO_4$ concentrated, $CHCl_3$, -5 ºC, 82%
b: $POCl_3$, 150 ºC, reflux, 8 hours, 54%
c: $POCl_3$, MW, 300W, 20 min, 47%

Scheme 1. Synthetic routes already published for 4,5-Dicyanopyridazine (DCP).

2. Results and Discussion

All compounds were synthetized as expected. ^{1}H NMR and ^{13}C NMR spectra and mass spectra are according to Ruggiero and co-workers [6]. IR spectra of compound **3** shown a characteristic ester bands at 1735 cm^{-1} (C=O) and 1302 cm^{-1} (C–O). IR spectra of compound **2** ester characteristic bands disappearing and new bands at 1670 cm^{-1} (C=O) and 3070-3376 cm^{-1} (NH_2 – primary amine) appears.

Better results and yields were achieved changing CH_2Cl_2 for $CHCl_3$, because of better stabilization of radicals in first step of synthesis. The microwave synthesis considerably optimized the time of the third synthetic step, being only 20 minutes against 7-8 hours in traditional way.

3. Material and Methods

3.1 Experimental

Pyridazine (**4**) ethyl pyruvate $FeSO_4.7H_2O$ and chloroform were purchased from Aldrich. Sulfuric acid, 30% aqueous H_2O_2, methanol and Reagents were used as received without further purification and solvents were dried.

^{1}H NMR and ^{13}C NMR spectra were obtained on Varian 500 MHz. Mass spectra were performed using HPLC-ESI-MS Agilent Technologies 1290 Infinity equipment composed of four modules, the quaternary pump, automatic injector and thermostatic column oven and was coupled to an Agilent Technologies Electrospray Mass Spectrometer, model 6130 Quadrupole. FTIR spectra were recorded on Varian IR-600 Infrared Spectrometer as KBr pellets. Microwave-assisted syntheses were carried out using mono mode CEM-Discover System microwave apparatus, model 908005.

3.2 Synthesis

*3.2.1 Diethyl pyridazine-4,5-dicarboxylate (**3**)*

30% aqueous H_2O_2 (3.43 g, 0.03 mol) was added dropwise with stirring to ethyl pyruvate (5.22 g, 0.045 mol) at -10°C. After 20 minutes, the solution was added dropwise at -5 °C to a well stirred mixture of pyridazine (**4**) (0.8 g, 0.01 mol), $FeSO_4.7H_2O$ (8.33 g, 0.03 mol), concentrated H_2SO_4 (1.6 mL, 0.015 mol), H_2O (4 mL) and $CHCl_3$ (30 mL). After 15 minutes, the mixture was added to ice water and extracted with $CHCl_3$ (5 x 20 mL). The organic layer was washed with H_2O (25 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (CH_2Cl_2 : EtOAc - 5:1) afforded compound **3** (1,82 g, 82%) as a yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.0 Hz, 6H), 4.45 (q, *J* = 7.0 Hz, 4H), 9.49 (s, 2H); : ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.88, 63.02, 128.12, 149.12, 163.64; MS (ESI) *m/z*: Calculated: 224.0; Found: 225.0 [M + H]$^+$; IR (KBr): ν_{max}/cm^{-1}, 1735 (C=O) 1302 (C-O).

*3.2.2 Pyridazine-4,5-dicarboxamide (**2**)*

Compound **3** (0.108 g, 0.64 mmol) was added to a saturated methanolic NH_3 (60 mL) and the mixture allowed to stand for 4 days at room temperature. Solid precipitated was filtered off and washed with cold methanol and cold acetone, afforded compound **2** as a white solid (0.98 g, 94%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.03 (s, 2H), 7.34 (s, 2H), 8.49 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 131.87, 149.26, 165.81; MS (ESI) *m/z*: Calculated: 166.0; Found: 167.0 [M + H]$^+$; IR (KBr): ν_{max}/cm^{-1}, 3376, 3070 (N-H), 1670 (C=O).

*3.2.3 4,5-Dicyanopyridazine (**1**)*

In a glass sealed tube, under oxygen-free nitrogen atmosphere, diamide **2** (0.70 g, 3.1 mmol) was mixture with distilled $POCl_3$ (2 mL) about 40 minutes and the reaction was performed via microwave. It was irradiated at reflux at fix potency (300 W) and the temperature varied until 130°C, so it stabilizes. The excess of $POCl_3$ was removed by evaporation under reduced pressure. The residue was suspended in saturated aqueous Na_2CO_3 (15 mL) at 5 °C and the alkaline solution extracted with Et_2O (7 x 15 mL). The organic extracts were washed with brine (15 mL) and dried with $MgSO_4$. Rotary evaporation and chromatography (CH_2Cl_2 : EtOAc - 5 : 1) gave compound **1** (18 mg, 43 %) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 111.37, 114.31, 150.23; MS (ESI) *m/z*: Calculated: 130.0; Found: 130.1 $[M]^+$

4. Conclusions

Synthesis of phthalonitriles from DCP shown a great potential to synthetize new phthalocyanines. The main goal was achieved in the third step of DCP synthesis, what took few minutes, with good yields, compared with hours in another published method.

Acknowledgments

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