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EFFICIENT SYNTHESIS OF NEW POTENTIALLY BIOACTIVE TRICYCLIC PYRIDINONES

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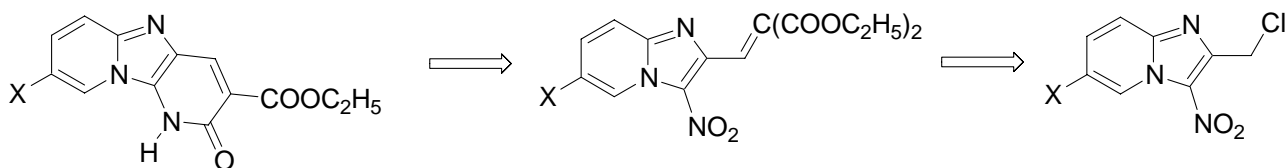
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Abstract – A rapid synthetic route towards new tricyclic pyridinones, from 6-halogeno-3-nitroimidazo[1,2-*a*]pyridines bearing the diethyl methylenemalonate group at the 2-position or directly from 6-halogeno-3-nitroimidazo[1,2-*a*]pyridines bearing the diethyl methylmalonate group at the 2-position, is described.

INTRODUCTION

Huperzine A,¹ a lycopodium alkaloid, is a tricyclic pyridinone, which is a potent, reversible acetylcholinesterase inhibitor with excellent penetration into the central nervous system and recent findings suggest that Huperzine A may be a unique and important drug for the treatment of Alzheimer's disease patients.² A synthesis of tricyclic pyridinones has been the subject of several recent reports, because they are interesting intermediates in the syntheses of important drugs or drug candidates as for example, the anti-tumor agent (+)-camptothecin,³ benzodiazepine receptors ligands⁴⁻⁶ or subtype-selective GABA_A receptor antagonists.⁷ Various syntheses are developed to find new compounds of potential pharmaceutical interest with improved biological activities.⁸⁻¹⁹

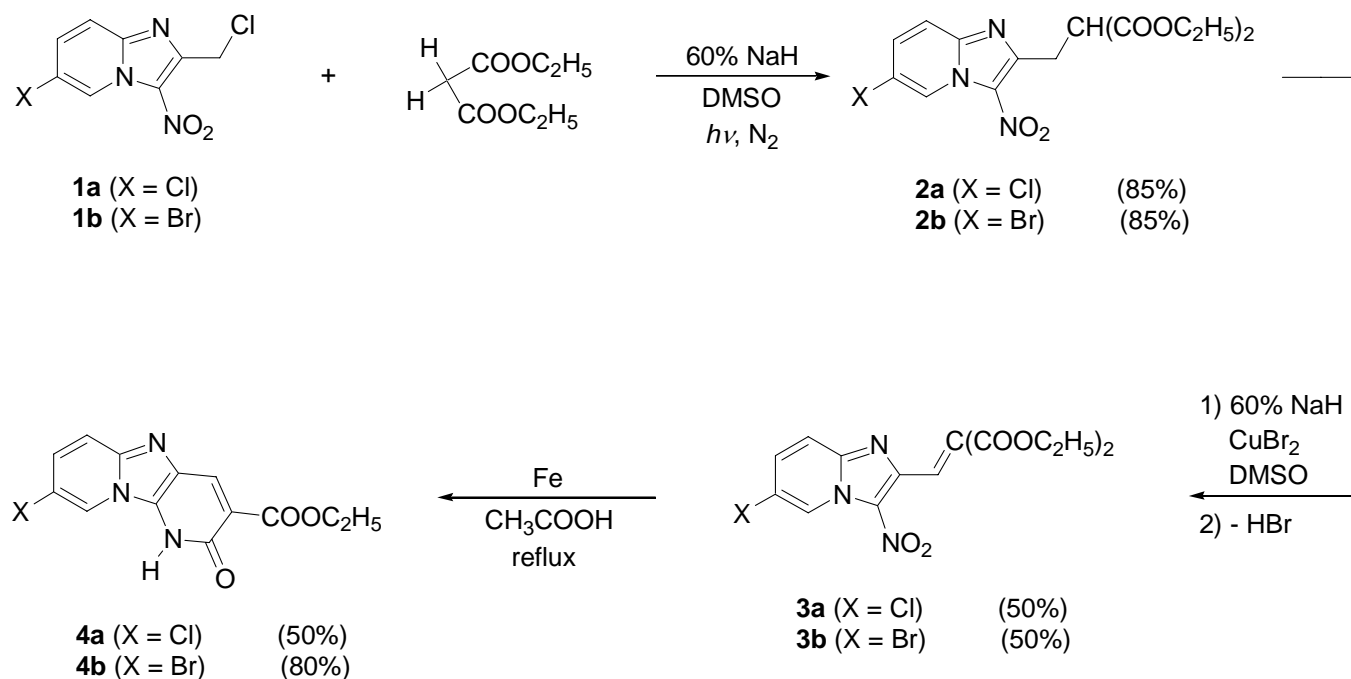
In continuation of our study of the reactivity of 6-halogeno-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridines in electron transfer reactions²⁰⁻²² and as part of a program directed to the synthesis of new tricyclic pyridinones of pharmaceutical interest bearing an ester group at the 3-position, we required 6-halogeno-3-nitroimidazo[1,2-*a*]pyridines bearing the diethyl methylenemalonate group at the 2-position feasible by the following retrosynthetic scheme (Scheme 1).



Scheme 1

Before this work, only the diethyl 2-(3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3**) ($X = H$), had been prepared in 20% yield from 2-benzenesulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridine and diethyl ketomalonate by an original direct Julia olefination.²³

To find a new synthesis of compounds (**3**) with improved yield, we decided to investigate the $S_{RN}1$ reaction of diethyl malonate anion with 6-halogeno-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridines (**1a**) and (**1b**) followed by the formation of the double bond by using a mild halogenation of stabilized ester enolates by cupric bromide²⁴ and hydrogen bromide elimination (Scheme 2).



Scheme 2

RESULTS AND DISCUSSION

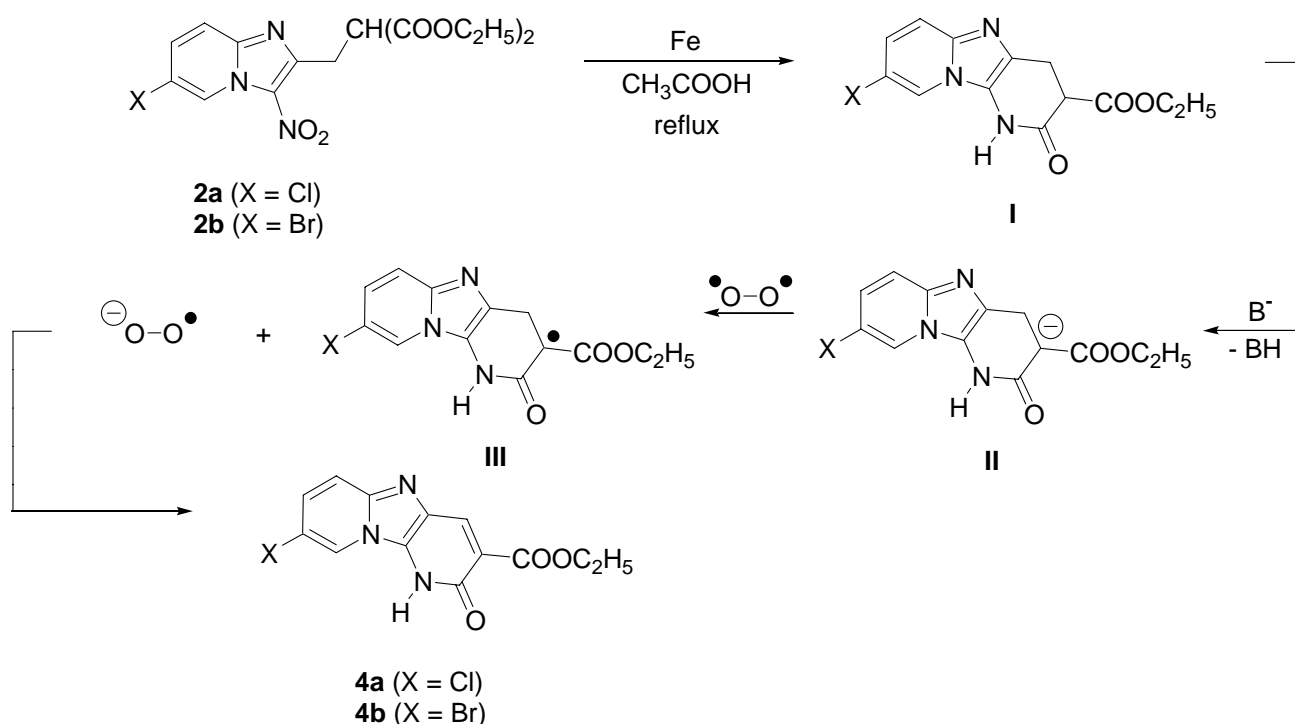
As expected, the $S_{RN}1$ reaction of sodium enolate of diethyl malonate with 6-halogeno-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridines (**1a**) and (**1b**) in DMSO under nitrogen with photostimulation gave the corresponding diesters (**2a**) and (**2b**) in good yields (85%).²⁰ As already shown,²⁰ only the chloromethyl group was found to be reactive under these experimental conditions. To our satisfaction, the reaction of two equivalents of cupric bromide with the preformed sodium enolates of **2a** and **2b** led directly to the desired ethylenic diesters (**3a**) and (**3b**) in moderate yields (50%).

The tricyclic moiety was formed in a one-pot reduction-cyclization by heating ethylenic diester derivatives (**3a**) and (**3b**) in glacial acetic acid under reflux with an excess of iron powder (14 equiv.) for 2 h. After treatment, the corresponding tricyclic pyridinones (**4a**) and (**4b**) were obtained respectively in 50 and 80% yields (Scheme 2).

We have found, somewhat serendipitously, in trying to prepare the tricyclic tetrahydropyridinones (**I**) (Scheme 3), that a one-pot synthesis of **4a** and **4b** can be directly processed from **2a** and **2b**. After heating of diester derivatives (**2a**) and (**2b**) in glacial acetic acid under reflux with an excess of iron powder (14 equiv.) for 24 h, filtration through a short Celite column and evaporation of acetic acid under reduced pressure, the residue was neutralized with a saturated solution of Na_2CO_3 at room temperature on exposure to the air. After extraction with CHCl_3 , the solution was dried over MgSO_4 , the solvent was evaporated under reduced pressure to give the target lactams (**4a**) and (**4b**) in respectively 50 and 74% yields and not the firstly expected tetrahydropyridinones (**I**).

The formation of a dihydropyridinone from a tetrahydropyridinone in basic medium in the presence of air has been studied in the one-step preparation of functionalized 3-cyano-2-pyridinones by Ciufolini and coworkers.^{25,26} Such simplified mechanistic picture for the pyridinone-forming process applied to **2a** and **2b** is reported in the following scheme (Scheme 3).

The cyclic intermediate (**I**) in presence of base gives anion (**II**). Single electron transfer (SET) from **II** to O_2 yields radical (**III**) and aromatization of **III** by hydrogen abstraction gives the corresponding tricyclic pyridinones (**4a**) and (**4b**).



Scheme 3

In conclusion, we have developed the rapid synthetic route towards the new tricyclic pyridinones (**4a**) and (**4b**) from 6-halogeno-3-nitroimidazo[1,2-*a*]pyridines (**3a**) and (**3b**) bearing the diethyl methylenemalonate group at the 2-position or directly from 6-halogeno-3-nitroimidazo[1,2-*a*]pyridines (**2a**) and (**2b**) bearing the diethyl methylmalonate group at the 2-position. These results extend the availability and scope of functionalized tricyclic pyridinones.

EXPERIMENTAL

General Methods. Melting points were determined with a B-540 Büchi melting point apparatus. 200 MHz ^1H NMR and 50 MHz ^{13}C NMR spectra were recorded on a Bruker ARX 200 spectrometer in CDCl_3 solution at the Faculté de Pharmacie de Marseille. ^1H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to CHCl_3 7.26 ppm (^1H) and 77.16 ppm (^{13}C). Elemental analyses were carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme.

Diethyl 2-(6-chloro-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3a**).

To a solution of 0.5 g (1.35 mmol) of diethyl 2-(6-chloro-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethyl)malonate (**2a**)²⁰ in DMSO (2 mL) was added 0.081 g (2.3 mmol) of 60% NaH and the mixture was stirred 0.5 h at rt. To this solution, 0.91 g (4.06 mmol) of CuBr_2 was added and the disappearance of **2a** was monitored by TLC. After disappearance of **2a**, cold water was added to the reaction mixture and a precipitate was formed. After filtration, drying of the solid and crystallization from isopropanol, diethyl 2-(6-chloro-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3a**) was obtained as a white solid in 50% yield (250 mg). mp 162.3 °C. ^1H NMR (CDCl_3) δ 1.37 (t, $J = 7.1$ Hz, 6H, 2x CH_3); 4.36 (q, $J = 7.1$ Hz, 2H, CH_2); 4.43 (q, $J = 7.1$ Hz, 2H, CH_2); 7.60 (dd, $J = 1.9$ Hz, $J = 9.5$ Hz, 1H, H_7); 7.67 (d, $J = 9.5$ Hz, 1H, H_8); 8.42 (s, 1H, CH); 9.47 (dd, $J = 0.9$ Hz, 1H, H_5). ^{13}C NMR (CDCl_3) δ 14.0 (CH_3); 14.1 (CH_3); 61.8 (CH_2); 62.3 (CH_2); 118.9 (CH); 124.1 (C); 125.5 (CH); 125.7 (C); 128.6 (CH); 132.4 (CH); 160.7 (C). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_6\text{Cl}$: C, 48.99; H, 3.84; N, 11.43 Found: C, 48.91; H, 3.95; N, 11.22.

Diethyl 2-(6-bromo-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3b**).

Following the procedure described for **3a** derivative, diethyl 2-(6-bromo-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3b**) was obtained as a light yellow solid in 50% yield (280 mg). mp 163.3 °C. ^1H NMR (CDCl_3) δ 1.36 (t, $J = 7.2$ Hz, 3H, CH_3); 1.37 (t, $J = 7.2$ Hz, 3H, CH_3); 4.36 (q, $J = 7.2$ Hz, 2H, CH_2); 4.43 (q, $J = 7.2$ Hz, 2H, CH_2); 7.61 (dd, $J = 0.9$ Hz, $J = 9.4$ Hz, 1H, H_8); 7.71 (dd, $J = 1.9$ Hz, $J = 9.4$ Hz, 1H, H_7); 8.42 (s, 1H, CH); 9.57 (dd, $J = 0.9$ Hz, $J = 1.9$ Hz, 1H, H_5). ^{13}C NMR (CDCl_3) δ 14.0 (CH_3); 14.1 (CH_3); 61.7 (CH_2); 62.2 (CH_2); 112.3 (C); 119.1 (CH); 127.6 (CH); 128.6 (CH); 134.1 (C); 134.6 (CH); 142.0 (C); 143.2 (C). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_6\text{Br}$: C, 43.71; H, 3.42; N, 10.19. Found: C, 43.60; H, 3.33; N, 10.05.

Ethyl 8-chloro-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3',2'-*d*]imidazo-3-carboxylate (**4a**).

Method from **3a**. A solution of 60 mg (0.163 mmol) of diethyl 2-(6-chloro-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (**3a**) in glacial acetic acid (10 mL) was stirred and heated to reflux. To this solution was added iron powder 0.128 g (2.30 mmol) and the stirred mixture was heated under reflux 2 h. After cooling the solution was filtered through celite and celite was washed with glacial acetic acid. The acetic acid solution was then evaporated on a rotary evaporator and the residue basified with a saturated solution of Na₂CO₃. The aqueous layer was extracted with chloroform. The combined organic layer was dried over MgSO₄ and evaporated to give **4a** as a yellow solid in 50% yield (23 mg). The analytical sample of **4a** was obtained as a yellow solid by crystallization from isopropanol. Method from **2a**. A solution of 100 mg (0.270 mmol) of diethyl 2-(6-chloro-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethyl)malonate (**2a**) in glacial acetic acid (5 mL) was stirred and heated to reflux. To this solution was added 0.212 g (3.80 mmol) of iron powder and the stirred mixture was heated under reflux 24 h. After cooling the solution was filtered through celite and celite was washed with glacial acetic acid. The acetic acid solution was then evaporated on a rotary evaporator and the residue basified with a saturated solution of Na₂CO₃. The aqueous layer was extracted with chloroform. The combined organic layer was dried over MgSO₄ and evaporated to give **4a** as a yellow solid in 50% yield (39 mg). mp 207.8 °C. ¹H NMR (CDCl₃) δ 1.49 (t, *J* = 7.0 Hz, 3H, CH₃); 4.53 (q, *J* = 7.0 Hz, 2H, CH₂); 7.39 (d, *J* = 9.8 Hz, 1H, H₇); 7.57 (d, *J* = 9.8 Hz, 1H, H₈); 8.67 (s, 1H, H₅); 8.81 (s, 1H, CH); 11.90 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 14.1 (CH₃); 62.6 (CH₂); 107.7 (C); 119.0 (CH); 119.8 (C); 122.4 (CH); 131.4 (C); 132.1 (CH); 132.8 (CH); 142.8 (C); 147.1 (C); 161.5 (C); 169.6 (C). Anal. Calcd for C₁₃H₁₀N₃O₃Cl: C, 53.53; H, 3.46; N, 14.41. Found: C, 53.80; H, 3.46; N, 14.32.

Ethyl 8-bromo-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3',2'-*d*]imidazo-3-carboxylate (4b**).**

Following the procedures described for **4a** derivative, ethyl 8-bromo-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3',2'-*d*]imidazo-3-carboxylate (**4b**) was obtained as a green solid in 80% (39 mg) (method from **3b**) and 74% (60 mg) yields (method from **2b**). The analytical sample of **4b** was obtained as a green solid by crystallization from isopropanol. mp 209 °C. ¹H NMR (CDCl₃) δ 1.49 (t, *J* = 7.1 Hz, 3H, CH₃); 4.53 (q, *J* = 7.1 Hz, 2H, CH₂); 7.46 (dd, *J* = 1.7 Hz, *J* = 9.8 Hz, 1H, H₇); 7.52 (dd, *J* = 1.0 Hz, *J* = 9.8 Hz, 1H, H₈); 8.80 (dd, *J* = 1.0 Hz, *J* = 1.7 Hz, 1H, H₅); 8.81 (s, 1H, CH); 11.90 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 14.2 (CH₃); 62.7 (CH₂); 106.0 (C); 107.7 (C); 119.2 (CH); 124.8 (CH); 131.2 (C); 132.8 (CH); 134.0 (CH); 147.1 (C); 161.5 (C); 169.6 (C). Anal. Calcd for C₁₃H₁₀N₃O₃Br: C, 46.45; H, 3.00; N, 12.50. Found: C, 46.49; H, 3.08; N, 12.49.

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