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SYNTHESIS OF A NEW IMIDAZO[4,5-*b*]PYRIDIN-5-ONE *VIA* A VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN

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Abstract – A new imidazo[4,5-*b*]pyridin-5-one was prepared in five steps from 4(5)-nitro-1*H*-imidazole *via* a vicarious nucleophilic substitution of hydrogen of 1-benzyl-4-nitro-1*H*-imidazole with the carbanion generated from chloroform and potassium *tert*-butoxide. Hydrolysis of 1-benzyl-5-dichloromethyl-4-nitro-1*H*-imidazole and Knoevenagel condensation between the resulting aldehyde and diethyl malonate catalyzed by titanium(IV) chloride gave the corresponding 4-nitroimidazole bearing at 4 position the diethyl methylenemalonate group. Reduction and cyclization afforded the required ethyl 1-benzyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate.

INTRODUCTION

In continuation of our studies of the reactivity of sulfonyl carbanions in electron transfer reactions[1,2] and as part of a program directed to the synthesis of new pyridinones of pharmaceutical interest for the treatment of insomnia, anxiety, schizophrenia and Alzheimer's disease, we have recently disclosed, from nitroheterocyclic sulfones prepared by vicarious nucleophilic substitution of hydrogen, a new synthetic approach involving a direct Julia olefination between the anions of 1,2-dialkyl-4-phenylsulfonylmethyl-5-nitro-1*H*-imidazoles and diethyl ketomalonate, which affords, in a one-pot reaction, original 5-nitroimidazoles bearing the diethyl methylenemalonate group at 4 position.[3] (Figure 1)

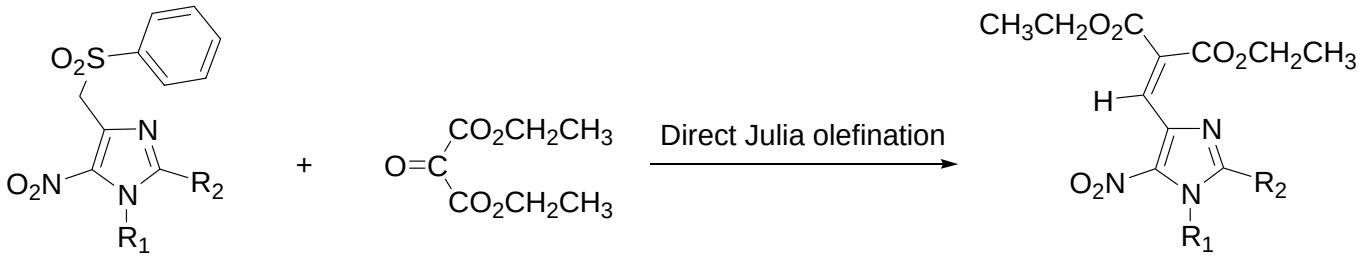


Figure 1. Synthesis of diethyl 2-(1,2-dialkyl-5-nitro-1*H*-imidazol-4-ylmethylene)malonates by direct Julia olefination.

Unfortunately, in 4-nitroimidazole series, 5-benzenesulfonylmethyl-1-methyl-4-nitro-1*H*-imidazole[4] (R_1 = CH_3, R_2 = H) and 5-benzenesulfonylmethyl-1,2-dimethyl-4-nitro-1*H*-imidazole[4] (R_1 = CH_3, R_2 = CH_3) prepared by vicarious nucleophilic substitution of hydrogen were found to be unreactive in this direct olefination with diethyl ketomalonate, probably for steric hindrance of nitro and methyl groups (Figure 2).

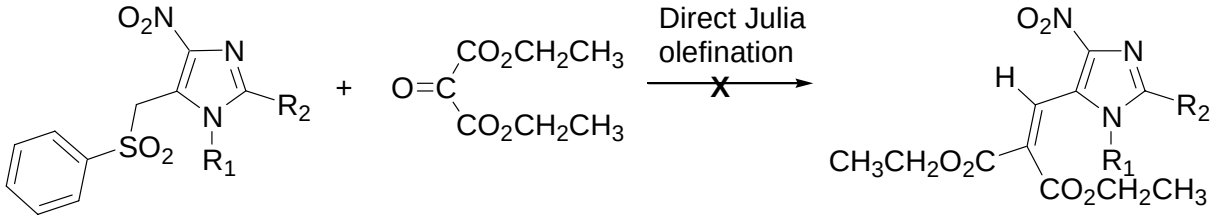


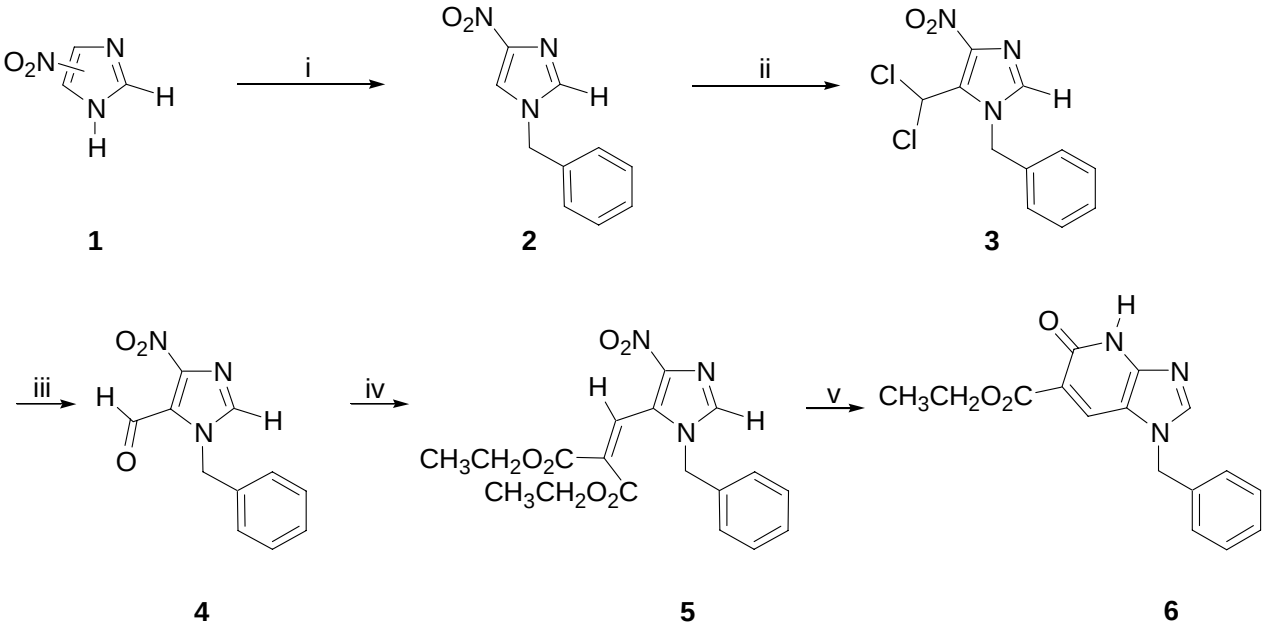
Figure 2. Failure of the direct Julia olefination in 4-nitroimidazole series.

Thanks again to vicarious nucleophilic substitution of hydrogen, the preparation of a 4-nitroimidazole bearing the diethyl methylenemalonate group at 5 position seemed possible *via* a vicarious nucleophilic substitution of hydrogen with chloroform from **2**, hydrolysis of the dichloromethyl derivative (**3**) in aldehyde (**4**) and Knoevenagel condensation with diethyl malonate affords the desired compound (**5**) as described in the Scheme.

RESULTS AND DISCUSSION

Herein, we describe the synthesis of **5** (Scheme) starting from the commercially available 4(5)-nitro-1*H*-imidazole (**1**) and the preparation of the firstly required ethyl 1-benzyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**6**) (Scheme). Condensation of **1** with benzyl chloride in a mixture of acetic acid and DMF at 140 °C gave the expected 1-benzyl-4-nitro-1*H*-imidazole (**2**)[5] in 27% yield. Treatment of **1** with benzyl chloride in DMF in presence of K_2CO_3 at 75 °C during 4 h was also tried. Contrary to Chen and coworkers,[6] in our hands, under the same experimental conditions, we got a

compound in 67% yield, which is the 1-benzyl-4-nitro-1*H*-imidazole (**2**) and not the 1-benzyl-5-nitro-1*H*-imidazole obtained by Chen and coworkers. The ^{1}H NMR spectral data and the melting point of **2** are in agreement with the literature.[7-9]



Scheme. Reagents and conditions: (i) $C_6H_5CH_2Cl$, K_2CO_3, DMF, 75 °C, 4 h (67%). (ii) *t*-BuOK, THF-DMF, -78 °C, $CHCl_3$, N_2, 10 min, CH_3COOH-CH_3OH (72%). (iii) HCOOH-H_2O, 115 °C, 18 h (90%). (iv) THF, $TiCl_4$/ CH_2Cl_2, addition of **4**, $CH_2(CO_2CH_2CH_3)_2$, Pyridine, rt, 12 h, N_2 (59%). (v) Iron powder (14 eq.), CH_3CO_2H, reflux, 20 min (36%).

This result was expected because it is well established that 1-alkyl-4-nitro-1*H*-imidazoles are obtained from 4(5)-nitro-1*H*-imidazoles and alkyl halides in basic media.[10,11] Vicarious nucleophilic substitution of hydrogen of **2** with the anion generated from chloroform and potassium *tert*-butoxide at -78 °C afforded 1-benzyl-5-dichloromethyl-4-nitro-1*H*-imidazole (**3**)[11] in 72% yield. The structure of **3** was confirmed by X-Ray analysis (Figure 3).

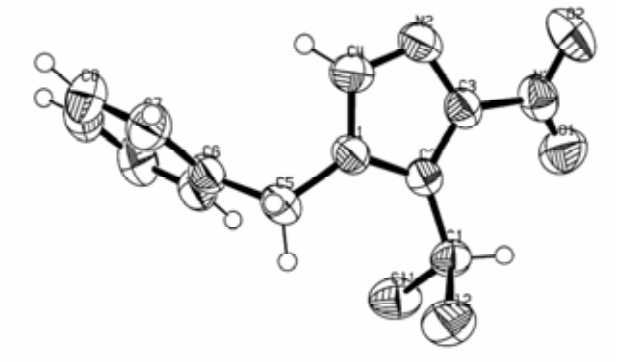


Figure 3. ORTEP plot of the 1-benzyl-5-dichloromethyl-4-nitro-1*H*-imidazole (**3**).

Hydrolysis of **3** with formic acid gave the aldehyde (**4**)[12] in 90% yield. The condensation of **4** with diethyl malonate anion formed from diethyl malonate by NaH in DMSO failed as the reaction of **4** with diethyl malonate in presence of piperidine in ethanol at reflux. The low reactivity of such an aldehyde in Knoevenagel condensation has been reported by Perandones.[13] Indeed, 5-amino-2,3-dimethyl-3*H*-imidazole-4-carbaldehyde after 10 h at reflux of methanol with diethyl malonate and sodium methoxide was found to be unreactive and the formation of the expected ethyl 1,2-dimethyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate was not observed. In contrast, the Knoevenagel reaction of **4** with diethyl malonate catalyzed by $TiCl_4$/pyridine[14,15] gave the desired diethyl 2-(3-benzyl-5-nitro-3*H*-imidazol-4-ylmethylene)malonate (**5**) in 59% yield.

Finally, treatment of **5** with an excess of iron powder in glacial acetic acid at reflux afforded the target molecule of this work, the ethyl 1-benzyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**6**), in 36% yield (Scheme).

Further functional group transformations of **6** could give new imidazo[4,5-*b*]pyridin-5-one derivatives of pharmaceutical interest.[13,16,17]

In conclusion, the previously unknown diethyl 2-(3-benzyl-5-nitro-3*H*-imidazol-4-ylmethylene)malonate (**5**) can be prepared from 4(5)-nitro-1*H*-imidazole *via* a vicarious nucleophilic substitution of hydrogen. Reduction and cyclization afforded the required ethyl 1-benzyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**6**). The imidazopyridinone is formed in only five steps from commercially available 4(5)-nitro-1*H*-imidazole, thus providing a new synthetic approach to this heterocyclic series with potential applications in medicinal chemistry.

EXPERIMENTAL

General Methods. Melting points were determined with a B-540 Büchi melting point apparatus. 300 MHz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 in $CDCl_3$ or DMSO-d_6 solution at the Centre Régional de RMN de la Faculté des Sciences et Techniques de Saint-Jérôme. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to $CHCl_3$ 7.26 ppm (^{1}H) 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. X-Ray analysis was carried out at the Laboratoire de Cristallochimie, UMR CNRS 6517, Faculté des Sciences et Techniques de Saint-Jérôme.

1-Benzyl-4-nitro-1*H*-imidazole (**2**). Following the procedure described in the reference 5, **2** was obtained in 27% yield. Following the procedure described in the reference 6, **2** was obtained in 67% yield. The analytical sample of **2** was obtained as a white solid by crystallization (diethyl ether/chloroform 3:1), mp 74 °C. ^{1}H NMR ($CDCl_3$) δ 5.10 (s, 2H, CH_2); 7.10-7.35 (m, 5H); 7.48 (s, 1H), 7.68 (s, 1H). ^{1}H NMR

(DMSO-d_6) δ 5.32 (s, 2H, CH_2); 7.39 (s, 5H); 8.01 (s, 1H); 8.50 (s, 1H). ^{13}C NMR(DMSO-d_6) δ 52.4 (CH_2); 123.2 (CH); 129.6 (2xCH); 130.0 (CH); 130.6 (2xCH); 137.9 (C); 139.1 (CH); 148.9 (C).

1-Benzyl-5-dichloromethyl-4-nitro-1*H*-imidazole (**3**). Following the procedure described in the reference 6, **3** was obtained after flash column chromatography of the crude product on silica gel (AcOEt/Hexane 1:3) in 72% yield. The analytical sample of **3** was obtained as a white solid by crystallization (hexane/chloroform), mp 82 °C. ^{1}H NMR ($CDCl_3$) δ 5.62 (s, 2H, CH_2); 7.27-7.48 (m, 5H); 7.78 (s, 1H); 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 51.7 (CH_2); 58.7 ($CHCl_2$); 127.6 (CH); 128.8 (2xCH); 129.7 (C); 129.8 (2xCH); 133.2 (C); 137.9 (CH). The C-NO_2 was not observed under these experimental conditions. Anal. Calcd for $C_{11}H_9N_3O_2Cl_2$: C. 46.18; H. 3.17; N. 14.69. Found: C. 46.05; H. 3.16; N. 14.67.

Data of X-Ray analysis.

Suitable crystals for X-Ray analysis were obtained by slow evaporation from a solution of chloroform at room temperature. Crystal size: 0.6x 0.5x 0.4 mm. Crystal color: colorless. Crystal description: prism. Crystal data for $C_{11}H_9N_3O_2Cl_2$: Mr = 286.11, orthorhombic, space group P n a 2_1, a = 9.3810 (2) Å, b = 22.6750 (5) Å, c = 5.9420 (10) Å, V = 1263.9(2) Å^3, Z = 4, D_c = 1.504 Mg m^{-3}, θ range for measured reflections θ = 2.35-26.33°, μ = 0.510 cm^{-1}, F(000) = 584, T = 293(2) K. Bruker-Nonius KappaCCD diffractometer,[18] data collected using Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELX97)[19] followed by full-matrix least-squares refinement (SHELXL97) on F^2 to final indices R_1 = 0.035 [$F_0^2 > 4\sigma(F_0^2)$] and wR_2 = 0.091 [$w = 1/[\sigma^2(F_0^2) + (0.0446P)^2 + 0.3989P]$ where $P = (F_0^2 + 2F_c^2)/3$. Final Fourrier peaks: ρ^+ = 0.226, ρ^- = -0.169.

CCDC 236135 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

3-Benzyl-5-nitro-3*H*-imidazole-4-carbaldehyde (**4**). A solution of 1 g (3.5 mmol) of **3** in formic acid (15 mL) and water (5 mL) was stirred at 115 °C for 18 h. After cooling, the solution was extracted with dichloromethane and dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **4** (0.727 g) in 90% yield. The analytical sample of **4** was obtained as a orange solid by crystallization (chloroform), mp 85 °C. ^{1}H NMR ($CDCl_3$), δ 5.50 (s, 2H, CH_2); 7.15-7.19 (m, 2H); 7.31-7.40 (m, 3H); 7.50 (s, 1H); 10.42 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 52.3 (CH_2); 127.4 (C); 128.4 (2xCH); 129.5 (CH); 129.7 (2xCH); 134.0 (CH); 139.3 (C); 145.8 (C); 181.9 (C=O). Anal. Calcd for $C_{11}H_9N_3O_3$: C. 57.14; H. 3.92; N. 18.17. Found: C. 57.30; H. 4.06; N. 18.29.

Diethyl 2-(3-benzyl-5-nitro-3*H*-imidazol-4-ylmethylene)malonate (**5**). Titanium(IV) chloride in dichloromethane (0.63 mL) was added dropwise to anhydrous THF (25 mL) under N_2 and the stirred

mixture was cooled in ice-bath. After 15 min, 0.380 g (2.26 mmol) of **4** in anhydrous THF (4 mL) and diethyl malonate (0.362 g; 2.26 mmol) in anhydrous THF (4 mL) were added. After 5 min, pyridine (0.8 mL, 10 mmol) in anhydrous THF (3 mL) was added dropwise and the reaction mixture was allowed to warm to ambient temperature and was stirred 12 h. The reaction was quenched with H_2O (6 mL) and Et_2O (6 mL), the organic layer was separated and the aqueous layer extracted with Et_2O (2x25 mL). The combined organic layer was washed with a saturated $NaHCO_3$ solution (2x25 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography eluting with chloroform/acetone (95:5) to give **5** as solid (0.470 g) in 59% yield. The analytical sample of **5** was obtained as a brown solid by crystallization (isopropanol), mp 116.4 °C. ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.2 Hz, 3H, CH_3); 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); 4.08 (q, *J* = 7.2 Hz, 2H, CH_2); 4.24 (q, *J* = 7.2 Hz, 2H, CH_2); 5.04 (s, 2H); 7.07-7.10 (m, 5H); 7.45 (s, 1H); 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3); 14.3 (CH_3); 51.0 (CH_2); 62.4 (CH_2); 62.6 (CH_2); 125.3 (C); 128.1 (2xCH); 129.5 (CH); 129.6 (CH); 129.7 (2xCH); 133.6 (C); 135.3 (C); 136.7 (CH); 162.9 (C=O); 163.7 (C=O). The C-NO_2 was not observed under these experimental conditions. Anal. Calcd for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.13; N, 11.25. Found: C, 58.07; H, 5.19; N, 10.77.

Ethyl 1-benzyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**6**). A solution of **5**, 0.15 g (0.4 mmol) in glacial acetic acid (6 mL) was stirred and refluxed. To this refluxing solution 0.31 g (5.62 atom/g) of iron powder was added portionwise and the mixture was refluxed for 20 min. 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 Na_2CO_3 solution. The aqueous layer was extracted with chloroform. The combined organic layer was dried ($MgSO_4$), and evaporated to give **6** (0.042 g) in 36% yield. The analytical sample of **6** was obtained as a white solid by crystallization (isopropanol), mp 205-206 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.3 Hz, 3H, CH_3); 4.42 (q, *J* = 7.3 Hz, 2H, CH_2); 5.35 (s, 2H); 7,35-7.40 (m, 5H); 8.12 (s, 1H), 8.14 (s, 1H), 11.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 50.1 (CH_2); 62.4 (CH_2); 104.9 (C); 121.2 (CH); 123.39 (CH); 127.6 (2xCH); 129.2 (CH); 129.6 (2x CH); 134.5 (C); 148.6 (C); 158.2 (C); 162.7 (C=O); 169.3 (C=O). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.67; H, 5.28; N, 14.08.

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