HETEROCYCLES, Vol. 70, 2006, pp. 201 - 205 . © The Japan Institute of Heterocdyclic Chemistry
Received, 19th May, 2006, Accepted, 13th July, 2006, Published online, 14th July, 2006. COM-06-S(W)4

DIRECT CONVERSION OF SUBSTITUTED PYRROLE-2-CARBOXYLIC ACID METHYL ESTERS TO THEIR 2-CARBONITRILE ANALOGUES

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Abstract – Small to large quantity (1-136 g) of substituted pyrrole-2-carbonitrles were reproducibly prepared from their corresponding 2-carboxylic acid methyl esters in one step with 53-61% yield and high chemical purity (>97%), with using dimethylaluminum amide [$(CH_3)_2AlNH_2$] that was freshly generated by treating anhydrous ammonia (NH_3) and trimethylaluminum [$(CH_3)_3Al$] at -40 ºC in chlorobenzene, a modified Weinreb's method.

The presence of a nitrile moiety on a pyrrole ring is found in a variety of molecules with wide spread interest, due to their pharmaceutical and agricultural biological properties,[1-4] as well as the development of new synthetic strategies.[5-8] In our efforts to prepare large quantities (>100 g) of 5-bromo-3-(4-fluorophenyl)-1-methyl-4-pyridin-4-yl-1*H*-pyrrole-2-carbonitrile (**4b**), we needed to start with its corresponding pyrrole-2-carboxylic acid methyl ester (**1b**). The original procedure followed a traditional multi-step approach (Scheme 1, Route A), that used a large excess of thionyl chloride (27.5 eq.) and phosphorus oxychloride (6.0 eq.).[1] For scale up purposes, large amounts of these reagents are inconvenient and present possible hazards. In contrast to the traditional synthesis, a few one-step processes are known for the direct conversion of carboxylic acid esters to their nitriles.[7, 9-11] For example, Weinreb's method, using commercially available trimethylaluminum and ammonia converts alkyl and aryl esters into nitriles in good to excellent yields (50-95%).[9,10] In 1998, Hwu and his colleagues demonstrated that aromatic esters, in particular indole-3-carboxylate could be directly converted to the corresponding nitriles in good yields (81-93%) after treating the esters with excess sodium bis(trimethylsilyl)amide in 1,3-dimethyl-2-imidazolidinone and tetrahydrofuran at 185 ºC for 24 hours in

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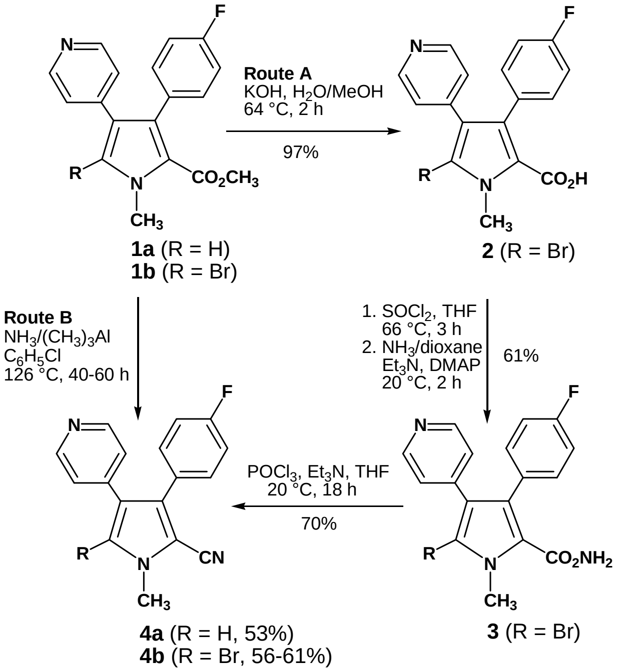
This paper is dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.

a sealed tube.[7] However, this method is limited in scope for scale up due to its need for hydroxy- or methoxy-substituted aromatic esters, the technical difficulty of monitoring the progress of the reaction, as well as sealed containment safety consideration for laboratory use. More recently, a high temperature (320-450 ºC) gas-phase catalytic reaction patent was reported that directly converts carboxylic acids esters to the desired nitriles in good yields (>82%), using ammonia in the presence of Ga_2O_3/SiO_2 (Ga/Si = 0.013) as catalysts.[11] This industrial production condition is again limited use for general laboratory preparation of nitriles. Since the direct conversions of substituted pyrrole-2-carboxylic acid methyl esters (**1a**) and (**1b**) to their corresponding pyrrole-2-carbonitriles (**4a**/**4b**) have not been reported, we describe the preparation of **4a** and **4b** under modified Weinreb's conditions (Scheme 1, Route B).



Scheme 1

Weinreb's $(CH_3)_3Al\text{-}NH_3$ method for the transformation of esters into nitriles used xylene as the solvent of choice.[9] In a modification of this method for lactones, 1,1,2-trichloroethane was selected as the reaction solvent.[10] For our purposes, chlorobenzene (bp = 132 ºC) was chosen as the solvent due to a poor solubility of both pyrrole-2-carboxylic acid methyl esters (**1a**) and (**1b**) in toluene or xylene. The preparation of $(CH_3)_2AlNH_2$ was accomplished by treating a chlorobenzene solution of condensed anhydrous ammonia (NH_3) with 2.0 M solution of trimethylaluminum [$(CH_3)_3Al$] at -40 ºC and then gradually warmed to 80 ºC.[9,10] In a pilot reaction, 5-unsubstituted pyrrole-2-carboxylic acid methyl ester (**1a**) was chosen to test the modified reaction condition, and 2-carbonitrile product (**4a**) was obtained in 53% isolated yield and high chemical purity (98.6%) together with a 3.0% of **1a** recovered, after the reaction was refluxed for 60 h (Table 1, Entry 1). Followed the success of direct transformation of **4a** from **1a**, 5-bromopyrrole-2-carboxylic acid methyl ester (**1b**) was further taken for scale up. Therefore, a solution of **1b** in chlorobenzene was added to a freshly prepared $(CH_3)_2AlNH_2$ solution and the mixture was refluxed for 40-60 h. The desired 5-bromopyrrole-2-carbonitrile (**4b**) product was obtained as a light gray-brown solid after chromatographic purification. The results of scale up reactions are shown as in Table 1 (Entries 2-5).

Table 1. The results of direct conversion of pyrrole-2-carboxylic acid methyl esters to 2-carbonitriles**.**

Entry	Esters (**1**) g (mol)	Reagents $NH_3/(CH_3)_3Al$ (eq./eq.)	Conditions	Nitrles (**4**)/Esters (**1**) g (yield %)	Chemical purity (%)
1	2.0 (0.0065)[a]	10.0/2.5	128 ºC, 60 h	0.95 (53.0)[c]/0.06 (3.0)[a]	98.6[f]
2	15.34 (0.039)[b]	5.4/2.5	128 ºC, 42 h	7.85 (56.0)[d]/0.88 (5.7)[b]	97.3[f]
3	107.0 (0.275)[b]	6.85/2.3	128 ºC, 60 h	52.65 (56.0)[d]/4.9 (4.6)[b]	99.0[f]
4	112.8 (0.290)[b]	8.10/2.2	120 ºC, 41 h	62.9 (61.0)[d]/3.4 (3.0)[b]	97.0[f]
5	282.75 (0.726)[b]	36.1/7.0	120 ºC, 60 h	136.8 (53.0)[d]/NA[e]	99.0[f]

[a]Compound (**1a**), R = H. [b]Compound (**1b**), R = Br. [c]Compound (**4a**), R = H. [d]Compound (**4b**), R = Br. [e]Not available. [f]Determined by HPLC analysis (area%).

In summary, with using less hazardous, lower cost reagents and solvent, a small quantity of 5-unsubstituted pyrrole-2-carbonitrle (**4a**) (~ 1.0 g) and large quantities (8.0-136.0 g) of 5-bromopyrrole-2-carbonitrle (**4b**) were prepared directly from their corresponding 2-carboxylic acid methyl esters (**1a**) and (**1b**), using a modified Weinreb's method in moderate to good and reproducible isolated yield (53-61%) and high chemical purity (>97%). In addition, 3.0-5.7% of the starting esters (**1a**)/(**1b**) were recovered from chromatographic purifications of the crude products. The conversion was completed after 40 h, extending the reaction time (Entries 1, 3, and 5) or charging more reagents ($NH_3/(CH_3)_3Al$) did not improve the yield (Entry 5). Furthermore, the progress of the reaction was easily monitored by either TLC or HPLC, and the presence of halogen (Br or F) or pyridinyl substituents on the pyrrole ring did not interfere with the reaction, which add value to this method as a convenient, scaleable alternate route for the preparation of pyrrole carbonitrile derivatives such as **4a** and **4b**.

EXPERIMENTAL

All reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz on a Bruker Avance-300 or 400 instruments; chemical shifts are reported with tetramethylsilane as an internal reference and the spectra were acquired at ambient temperature in DMSO-d_6. Mass spectra were recorded on an Agilent Series 1100 LC/MS instrument. Analytical HPLC analyses were performed on an Agilent Series 1100 system with an Agilent ZORBAX Ecilipse XDB-C_{18} column (4.6 x 150 mm, 3.5 micron) at 40°C with flow rate of 1.0 mL/min and run time of 17.0 min; monitoring wavelength at 215 and 254 nm. Solvents: A 0.05% TFA + H_2O, B 40% MeOH. Gradient of B: 55%/0.0 min, 55%/5.0 min, 70%/10.0 min, 70%/14.5 min, 55%/14.6 min, and 55%/17.0 min.

A Typical Procedure: A 5-L 4-neck reaction vessel was equipped with a thermocouple controller, an overhead stirrer, a pressure-equalizing dropping funnel, a fritted gas dispersion tube, and a Dry-Ice condenser with a nitrogen inlet/outlet adapter. This vessel was charged with chlorobenzene (1200 mL) with agitation under nitrogen and the solution was cooled to -40 °C. Ammonia (anhydrous, 99.99%, 32.7 g, 1.88 mol, Aldrich) was bubbled into the solution for 46 min, followed the addition of trimethylaluminum (316.0 mL, 0.632 mol, 2.0 M in toluene) over a 25-min period. The mixture was warmed from -40 to 80 °C over a 1 h period and stirred for an additional hour. A solution of 2-carboxylic acid methyl ester (**1b**) (107.0 g, 0.275 mol) in C_6H_5Cl (220 mL) was added via the dropping funnel over a 5-min period and the reaction mixture was gradually heated to 126±2 °C for 40-60 h. The progress of the reaction was monitored by TLC (hexane/EtOAc/NH_4OH, 70/30/0.5) and HPLC (compound/retention time: pyrrole-2-carbonitrle (**4b**)/3.0 min; pyrrole-2-carboxylic acid methyl ester (**1b**)/3.9 min; chlorobenzene/12.0 min; toluene/12.3 min). The solution was cooled to 0 °C, diluted with CH_2Cl_2 (1200 mL), and quenched very carefully with an aqueous NH_4Cl solution (101.4 g in 1200 mL of D.I. H_2O. Caution: this is an exothermic process, which releases methane gas. The first 100 mL of aqueous NH_4Cl solution was added dropwise over a 15-min period or until the gas evolution ceased and the internal temperature was elevated from 0 to 12 °C over a 30-min period). The mixture was stirred for 30 min at 20 °C and diluted with CH_2Cl_2 (1200 mL). The organic phase was separated and the aqueous phase (pH $\geq$ 10) was extracted with CH_2Cl_2 (1200 mL). The combined organic phases were washed with brine (1000 mL), and the solvent was condensed *in vacuo* at 85 °C. The resulting crude (105.8 g) material was purified by flash silica gel chromatography (SiO_2, 2.0 kg (230-400 mesh), using hexane/EtOAc/NH_4OH: 80/20/0 to 60/40/0.2), which afforded 4.9 g (4.6% isolated recovery yield) of starting methyl ester (**1b**) and 52.65 g (56% uncorrected isolated yield) of pyrrole-2-carbonitrle (**4b**) as a light gray-brown solid. The chemical purity of compound (**4b**) was 99% analyzed by both HPLC and ^{1}H-NMR. ^{1}H-NMR (300 MHz, DMSO-d_6): 3.84 (s, 3 H), 7.13 (d, J = 6.8 Hz, 2 H), 7.23 (d, J = 6.7 Hz, 2 H), 7.25 (d, J = 5.5 Hz, 2 H), 8.54 (d, J = 5.6 Hz, 2 H). MS (m/z): 356 $[M]^+$, 358 $[M+2]^+$. Anal. Calcd for $C_{17}H_{11}N_3BrF$: C, 57.32; H, 3.11; N, 11.80; Br, 22.43; F, 5.33. Found: C, 57.11; H, 3.43; N, 11.59; Br, 22.09; F, 5.18.

In the same manner as the above described for **4b**, 5-unsubstituted pyrrole-2-carbonitrile (**4a)** (0.95 g, 53% yield, 98% chemical purity) was directly prepared from **1a** (2.0 g) after a chromatographic purification. ^{1}H-NMR (300 MHz, DMSO-d_6): 3.86 (s, 3 H), 7.06 (d, $J = 6.9$ Hz, 2 H), 7.19 (d, $J = 6.8$ Hz, 2 H), 7.23 (d, $J = 5.7$ Hz, 2 H), 7.72 (s, 1 H), 8.42 (d, $J = 5.6$ Hz, 2 H). MS (m/z): 278 $[M+H]^+$, 300 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{12}N_3F$: C, 73.63; H, 4.36; N, 15.15; F, 6.85. Found: C, 73.48; H, 4.49; N, 15.03; F, 6.54.

ACKNOWLEDGMENTS

The authors thank Drs. Paul F. Jackson and Xiaodong Fan for helpful discussions.

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