Tetrahedron Letters 53 (2012) 3853–3856

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient synthesis of 2-alkylpyridines using an alkylation/double decarboxylation strategy

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ARTICLE INFO

Article history:
Received 4 April 2012
Revised 27 April 2012
Accepted 10 May 2012
Available online 19 May 2012

Keywords:
Pyridine
Decarboxylation
Malonate
Alkylation
Alkyl halide

ABSTRACT

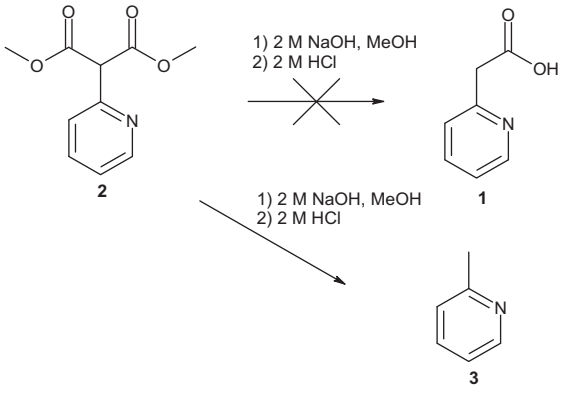
We have discovered a novel route for synthesising 2-alkylpyridines by exploiting the decarboxylation of pyridyl malonate esters. Herein we report the synthesis of a number of examples and describe how the reaction was discovered.

Pyridine rings are a common feature of many drug treatments currently on the market and remain an attractive moiety to medicinal chemists.[1] We were particularly interested in synthesising 2-alkylpyridines which are often accessed via cross-coupling methodology between alkyl halides and the corresponding pyridine-metal compound or 2-halopyridine and an alkyl metal.[2–4] Other approaches often used include alkylation of 2-methylpyridine, however this requires a strong base, for example, butyllithium.[5] Some strategies proceed via a pyridine-*N*-oxide,[6] although this requires subsequent reduction prior to product isolation.

Herein, we report a mild method for synthesising 2-alkylpyridines which potentially allows easier synthesis of compounds containing functional groups sensitive to strongly basic conditions. We recently had cause to synthesise 2-(2-pyridyl)acetic acid (**1**), however, attempts to synthesise this via hydrolysis and subsequent decarboxylation of dimethyl 2-(2-pyridyl)propanedioate (**2**) yielded doubly decarboxylated 2-methylpyridine (**3**) (Scheme 1).

We discovered that the decarboxylation is a known reaction in these systems,[7–9] however, we felt that this route might offer the possibility to introduce alkyl substitution by novel methodology at the 2-position of the pyridine ring, by exploiting the acidic nature of the proton alpha to the carbonyl groups.

To further investigate the scope of this methodology, 2-iodopyridine (**4**) was reacted with diethyl malonate using Kwong's conditions[10] to yield malonate ester **5** (Scheme 2). This was then alkylated with a range of alkyl bromides using either potassium carbonate or caesium carbonate in DMF at room temperature to furnish products **6a**–**h**, in good yields (Table 1).



Scheme 1. Observed decarboxylation of dimethyl 2-(2-pyridyl)propanedioate.

Hydrolysis of compounds **6a**–**h** with sodium hydroxide in MeOH afforded the sodium salts of the monocarboxylic acids which were not isolated. The second decarboxylation was not observed with either prolonged reaction time or heating using these basic conditions. To facilitate the second decarboxylation, the pH of the reaction mixture was critical. When the pH was adjusted to 1 by the addition of HCl no decarboxylation was observed, even after prolonged heating. Decarboxylation was effected by adjusting the pH of the reaction mixture to pH 4–5 by the addition of 1 M citric

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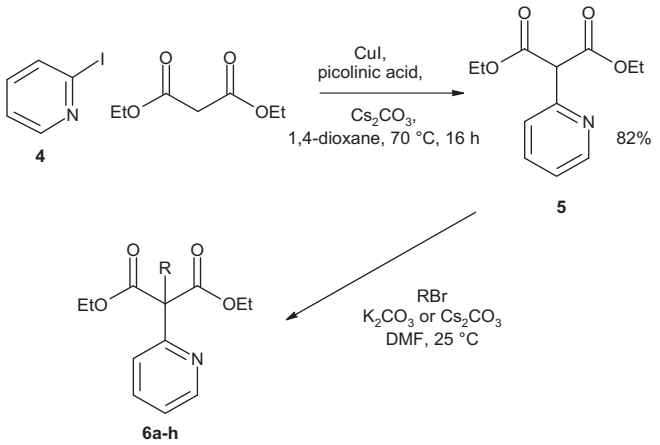
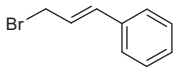
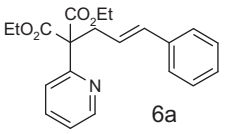
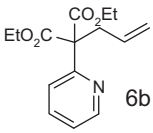
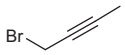
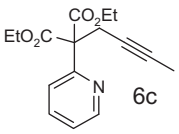
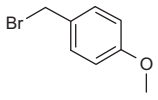
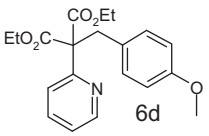
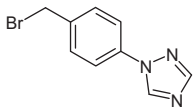
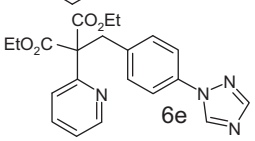
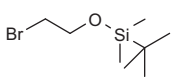
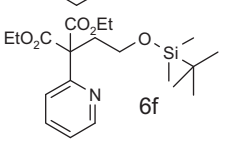
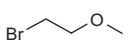
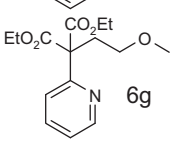
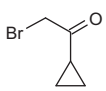
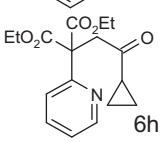
http://dx.doi.org/10.1016/j.tetlet.2012.05.049



4 5 6a-h

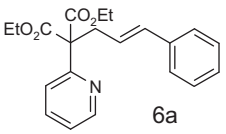
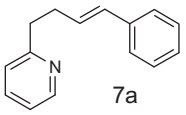
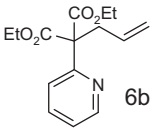
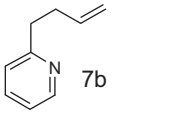
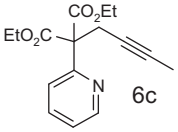
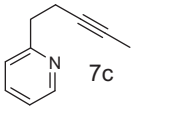
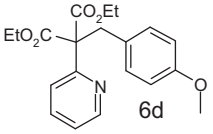
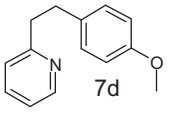
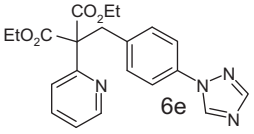
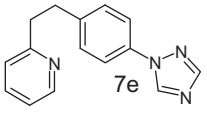
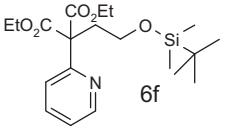
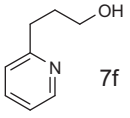
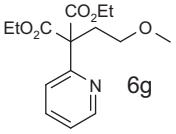
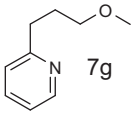
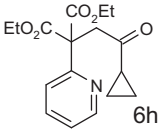
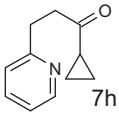
Scheme 2. General alkylation reaction scheme.

Table 1
Alkylation of diethyl 2-(2-pyridyl)propanedioate

Alkyl halide	Product	Yield[a] (%)
	 6a	93[b]
	 6b	87[c]
	 6c	85[b]
	 6d	75[c]
	 6e	44[c]
	 6f	61[c]
	 6g	35[b]
	 6h	61[c]

[a] Isolated yield.
[b] Cs_2CO_3 used as base.
[c] K_2CO_3 used as base.

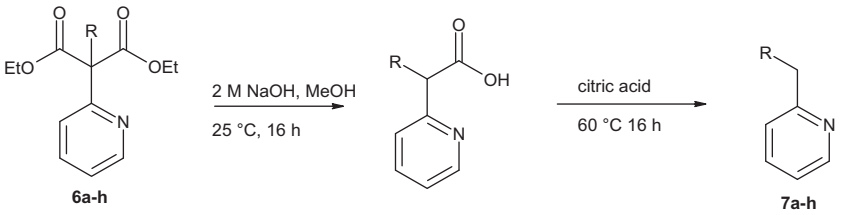
Table 2
Hydrolysis and double decarboxylation

Substrate	Product	Yield[a] (%)
 6a	 7a	96
 6b	 7b	73
 6c	 7c	71
 6d	 7d	79
 6e	 7e	81
 6f	 7f	90[b]
 6g	 7g	95
 6h	 7h	79

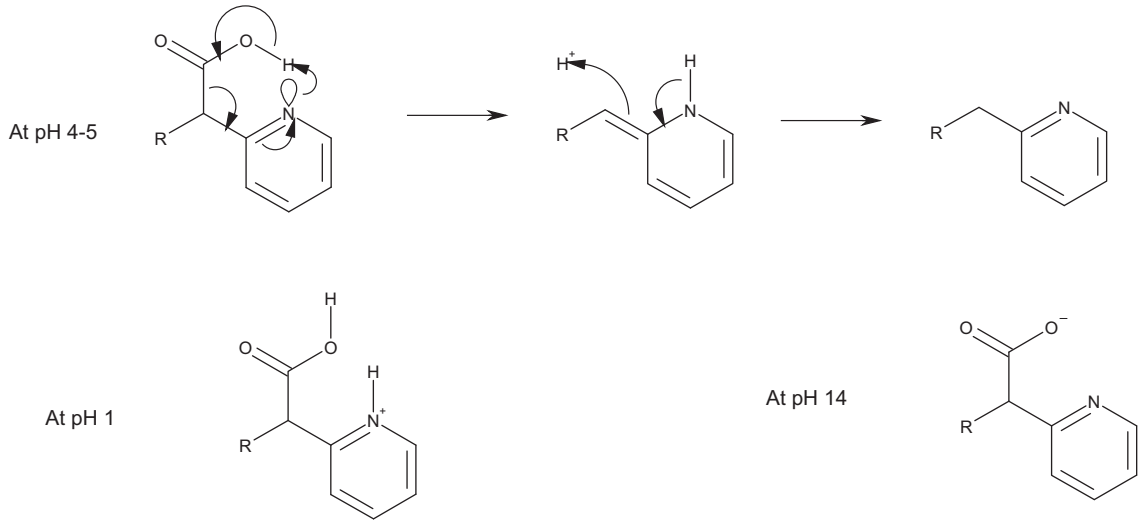
[a] Isolated yield.
[b] The silyl protecting group was unstable to the conditions.

acid and warming to 60 °C overnight (Scheme 3). This gave products **7a**–**h** shown in (Table 2).

A range of products was synthesised containing a number of different functional groups (Table 2). Olefins **7a** and **7b** were synthesised in good yields and this approach appears to offer an advantage over current methods available which tend to employ strongly basic or forcing conditions.[11,12] Phenethyl examples **7d** and **7e** could potentially be accessed from vinyl pyridine,[13,14] however starting materials will most likely be in short supply for this strategy. Alcohol **7f** might be synthesised by a number of methods including palladium chemistry,[15] however our approach avoids the use of heavy metal catalysis so may be more suited to larger scale routes. Perhaps one of the greatest advantages of this methodology is the ability to synthesise carbonyl-containing compounds such as ketone **7h**. We believe that it would be extremely challenging to access these types of compounds using the alternative methodologies described.



Scheme 3. General decarboxylation conditions.



Scheme 4. Mechanistic rationale for decarboxylation.

We postulate that the second decarboxylation proceeds at pH 4–5 as follows (Scheme 4). The lone pair on the nitrogen accepts the proton from the carboxylic acid which facilitates the concerted process to liberate carbon dioxide and generate the observed product. At pH 1, the nitrogen is protonated so the lone pair of electrons is unavailable to initiate this reaction. At pH 14 the acid is deprotonated and cannot therefore decarboxylate via this mechanism.

In summary we have presented a convenient method for the preparation of 2-alkylpyridine compounds. We have demonstrated that the methodology is versatile and tolerates a number of functional groups and so should be of interest to chemists interested in synthesising these types of compounds.

Preparation of diethyl 2-(pyridin-2-yl)malonate (5)

CuI (0.465 g, 2.44 mmol) was added to 2-iodopyridine (10 g, 48.78 mmol), diethyl malonate (15.63 g, 97.56 mmol), picolinic acid (0.601 g, 4.88 mmol) and Cs_2CO_3 (47.7 g, 146.34 mmol) in 1,4-dioxane (60 mL) under an atmosphere of nitrogen. The resulting suspension was heated to 70 °C and stirred for 16 h. The reaction mixture was allowed to cool to ambient temperature and was partitioned between EtOAc (300 mL) and saturated NH_4Cl (100 mL). The aqueous phase was separated and extracted with EtOAc (200 mL). The organic extracts were combined, dried over $MgSO_4$ and reduced to give an oil, which was purified by flash silica chromatography, elution gradient 0–40% EtOAc in heptane to afford diethyl 2-(pyridin-2-yl)malonate (**5**) (9.53 g, 82%) as an orange oil; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.17 (t, J = 7.1 Hz, 6H), 4.16 (qd, J = 7.1, 1.2 Hz, 4H), 5.07 (s, 1H), 7.35 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.4–7.45 (m, 1H), 7.82 (td, J = 7.7, 1.8 Hz, 1H), 8.51 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H); ^{13}C NMR (176 MHz, DMSO-d_6, 30 °C) 13.82, 59.63, 61.30, 123.04, 123.86, 136.86, 149.01, 153.12, 167.12; HRMS (ESI): MH^+, found 238.10727, $C_{12}H_{16}O_4N$ requires 238.10738.

Example procedure for the alkylation. Preparation of diethyl 2-allyl-2-(pyridin-2-yl)malonate (6b)

K_2CO_3 (583 mg, 4.21 mmol) was added in one portion to a mixture of diethyl 2-(pyridin-2-yl)malonate (**5**) (500 mg, 2.11 mmol) and 3-bromoprop-1-ene (510 mg, 4.21 mmol) in DMF (5 mL). The resulting suspension was stirred at ambient temperature for 16 h. The reaction mixture was evaporated to dryness, then the residue was partitioned between CH_2Cl_2 (25 mL) and H_2O (10 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to afford a crude product. This was purified by flash silica chromatography, elution gradient 0–50% EtOAc in heptane to give diethyl 2-allyl-2-(pyridin-2-yl)malonate (**6b**) (510 mg, 87%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.24 (t, J = 7.1 Hz, 6H), 3.11–3.15 (m, 2H), 4.24 (qd, J = 7.1, 3.8 Hz, 4H), 4.99 (t, J = 1.1 Hz, 1H), 5.01–5.05 (m, 1H), 5.72–5.85 (m, 1H), 7.18 (ddd, J = 6.7, 4.8, 1.7 Hz, 1H), 7.61–7.69 (m, 2H), 8.52–8.56 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 30 °C) 13.96, 40.20, 61.52, 65.33, 118.58, 122.31, 124.06, 133.27, 135.80, 148.66, 156.67, 169.65; HRMS (ESI): MH^+, found 278.13867, $C_{15}H_{20}O_4N$ requires 278.13868.

Example procedure for the decarboxylation. Preparation of 3-(pyridin-2-yl)propan-1-ol (7f)

2 M NaOH (1.510 mL, 3.02 mmol) was added to diethyl 2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-(pyridin-2-yl)malonate (**6f**) (239 mg, 0.60 mmol), in MeOH (5 mL). The resulting mixture was stirred at ambient temperature for 16 h. The solution was acidified

to pH 4 by addition of 1 M citric acid. The resulting mixture was heated to 60 °C and stirred overnight. The solution was allowed to cool to ambient temperature before MeOH was removed by evaporation. The residue was basified to pH 14 with 2 M NaOH. This aqueous mixture was extracted with CH_2Cl_2 (2×25 mL). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give 3-(pyridin-2-yl)propan-1-ol (**7f**) (75 mg, 90%) as an oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.95–2.04 (m, 2H), 2.96–3.01 (m, 2H), 3.72 (t, J = 5.8, 2H), 7.13 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.62 (td, J = 7.7, 1.8 Hz, 1H), 8.47–8.53 (m, 1H), OH not seen; ^{13}C NMR (101 MHz, $CDCl_3$, 30 °C) 31.78, 35.18, 62.12, 121.22, 123.25, 136.92, 148.60, 161.49; HRMS (ESI): MH^+, found 138.09119, $C_8H_{12}ON$ requires 138.09134.

Acknowledgments

We would like to thank Prof. Joe Sweeney for discussions and helping to plan the scope of this work. We would also like to thank Peter Barton, Howard Beeley, Paul Davey and Madeleine Vickers for analytical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.049.

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