Synthesis of tetrasubstituted pyridines by the acid-catalysed Bohlmann–Rahtz reaction

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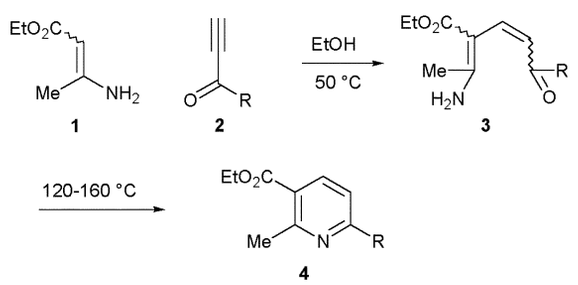
New facile experimental procedures for the preparation of 2,3,4,6-tetrasubstituted pyridines in a single synthetic step have been developed. Thus, an enamino ester and alkynone react by Michael addition–cyclodehydration in a heterocyclisation process that is catalysed by acetic acid, Amberlyst 15 ion exchange resin, zinc(II) bromide or ytterbium(III) triflate. The new one-step Brønsted or Lewis acid-catalysed Bohlmann–Rahtz reaction is a simple, direct and highly expedient method for the synthesis of pyridines that proceeds at a lower reaction temperature and avoids the need to isolate reaction intermediates.

Introduction

Simple nitrogen-containing heteroaromatic compounds have received a large amount of attention in the literature over the years. They are pharmacophores of considerable historical importance, have exciting biological properties in their own right and serve as important synthetic building blocks in drug discovery.[1] The pyridine nucleus has attracted a great deal of interest, mainly concerning the synthesis, reactions and biological properties of these heterocycles, as this structural motif appears in a large number of pharmaceutical agents and natural products.[2] Inevitably, with so many different methods available to the synthetic chemist to prepare pyridine-containing heterocycles, some procedures following their discovery will become largely forgotten. Bohlmann and Rahtz first reported a new synthesis of trisubstituted pyridines from ethyl β-aminocrotonate and ethynyl ketones back in 1957.[3] Since that date only a few reports on the use of this transformation have appeared in the literature. Moody has described the synthesis of the modified oxazole–thiazole–pyridine core of the promothiocin antibiotics[4–6] using a traditional Bohlmann–Rahtz reaction and a number of related heterocyclisations have been reported by Baldwin for the synthesis of novel heterocyclic substituted α-amino acids.[7] These reports establish the great potential of this reaction in natural product and heterocyclic chemistry but, in spite of these developments, no further improvements on the Bohlmann–Rahtz pyridine synthesis have appeared since its discovery and this reaction remains in very little use today.[8] This paper will address this shortfall in the current literature and describe new mild methods for a facile one-step Bohlmann–Rahtz pyridine synthesis so that this under-exploited process can find new use in synthetic chemistry.[9,10]

Results and discussion

The traditional Bohlmann–Rahtz pyridine synthesis is a two-step process involving, for example, initial Michael addition of ethyl β-aminocrotonate **1** and an ethynyl carbonyl compound **2** in ethanol at 50 °C. The aminodienone intermediate **3** is isolated and subsequently heated to high temperatures to affect cyclodehydration to pyridine **4** (Scheme 1).[3] Although the product usually needs purification, yields are good for this transformation and so the method offers considerable potential for application in heterocyclic chemistry. However, avoiding the use of high cyclodehydration temperatures, extending this protocol for use in the synthesis of tetrasubstituted pyridines and developing a single one-step experimental procedure would increase the scope and utility of the Bohlmann–Rahtz reaction. We set out to realise these goals by investigating the use of Brønsted and Lewis acid catalysts for the cyclodehydration of dienone **3a** (R = Me). An acid catalyst should promote the double bond isomerisation of this intermediate, resulting in spontaneous cyclodehydration at a lower reaction temperature, and thus obviating the need to isolate the conjugate addition product. If successful, this procedure then could be extended to provide a new and facile one-step method for the synthesis of tetrasubstituted pyridines.



Scheme 1 The traditional Bohlmann–Rahtz pyridine synthesis.

Aminoheptadienone **3a** was prepared by a standard Bohlmann–Rahtz reaction,[3] from ethyl β-aminocrotonate **1** and but-3-yn-2-one **2a** in ethanol at 50 °C to give the pure cyclodehydration precursor in 98% yield following purification. However, due to shortages in the availability of butynone **2a**, concerns about its volatility and in order to expand the scope of the traditional Bohlmann–Rahtz process, an alternative route to intermediate **3a** was sought. A mixture of ethyl β-aminocrotonate **1** and 4-(trimethylsilyl)but-3-yn-2-one **5a**, which was cheaper than **2a**, more readily available and less volatile, was heated to 50 °C in a range of different solvents (Table 1). In most cases only unreacted starting materials were isolated from the reaction mixture. However, when a solution of crotonate **1** and butynone **5a** was stirred in ethanol or DMSO at 50 °C for

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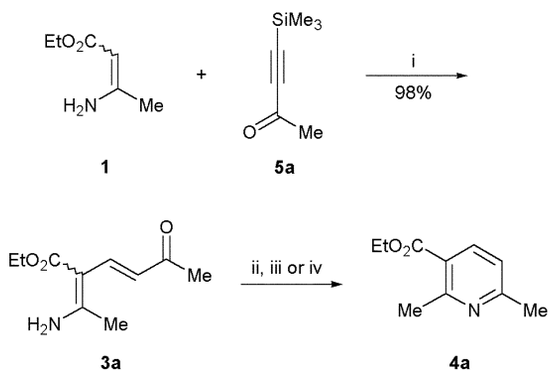
Table 1 Conditions investigated for the Michael addition of **1** and 4-(trimethylsilyl)but-3-yn-2-one **5a** in various solvents at 50 °C

Solvent	Result	Solvent	Result
Acetone	No reaction	Diethyl ether	No reaction
Toluene	No reaction	Neat	No reaction
DCM	No reaction	DMSO	Product **3a** (59%)
Chloroform	No reaction	Ethanol	Product **3a** (98%)

Table 2 The Lewis acid catalysed cyclodehydration of aminodienone **3a**

Lewis acid	Conditions	Compound
$BF_3{\cdot}OEt_2$	DCM, reflux, 4 h	**3a** (no reaction)
$FeCl_3$ (10 mol%)	DCM, reflux, 3.5 h	**3a**,**4a** (3 : 2)
$Sc(OTf)_3$ (100 mol%)	DCM, reflux, 24 h	**3a**,**4a** (1 : 3)
$ZnBr_2$ (100 mol%)	DCM, reflux, 24 h	**4a** (46%)
$ZnBr_2$ (15 mol%)	Toluene, reflux, 5 h	**4a** (59%)



Scheme 2 *Reagents*: i, EtOH, 50 °C, 5 h; ii, 140–150 °C (87%); iii, toluene–AcOH (5 : 1), RT, 2.5 h; then 50 °C, 1 h (quant.); iv, $ZnBr_2$ (15 mol%), toluene, reflux, 5 h (59%).

5 hours, aminodienone **3a** was produced in 98 or 59% yield, respectively, after purification. In both of these solvents desilylation occurred spontaneously under the reaction conditions. In view of the improvements that this transformation offered over the original procedure, this became the method of choice for the synthesis of aminodienone **3a** (Scheme 2).

When intermediate **3a** was heated in the absence of solvent, according to the standard Bohlmann–Rahtz cyclodehydration procedure,[3] pyridine **4a** was generated in 87% yield. This represented an overall yield for this transformation of 85% from crotonate **1**, including two chromatographic purifications, and this highlighted the great potential of the traditional procedure for the synthesis of trisubstituted pyridines. In order to improve on this process and reduce the temperature of the cyclodehydration reaction, a solution of intermediate **3a** was heated to 50 °C in toluene–acetic acid (5 : 1) to generate pyridine **4a** in quantitative yield and without any need for further purification (Scheme 2). Spectroscopic analysis of **4a** determined that it was indistinguishable from the product formed under the standard cyclodehydration conditions, namely heating to 160 °C and subsequent chromatographic purification on silica. This finding represented a considerable breakthrough in the search for a one-step Bohlmann–Rahtz protocol and confirmed that our initial premise was well justified.

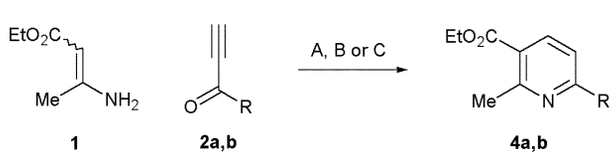
In the search for alternative methods to affect the cyclodehydration that were compatible with a range of functional groups, intermediate **3a** was reacted with a number of Lewis acids under a variety of conditions (Table 2). In general, the Lewis acid catalysed cyclodehydration appeared to be more sluggish and less efficient than the corresponding reaction conducted in acetic acid. However, using zinc(II) bromide (15 mol%) in toluene at reflux, pyridine **4a** was prepared in 59% yield, showing that a Lewis acid catalysed one-step Bohlmann–Rahtz reaction was feasible and warranted subsequent investigation.

Table 3 Comparing the three Bohlmann–Rahtz heteroannulation methods

Alkynone	R	Product	Method	Catalyst	Yield (%)
2a	Me	**4a**	A	None	85
2a	Me	**4a**	B	AcOH	77
2a	Me	**4a**	C	$ZnBr_2$	65
2b	Ph	**4b**	A	None	80
2b	Ph	**4b**	B	AcOH	85
2b	Ph	**4b**	C	$ZnBr_2$	86

With a range of successful conditions established for cyclodehydration at lower reaction temperatures, it remained to investigate whether these procedures were compatible with the initial Michael addition and so establish a new Bohlmann–Rahtz pyridine synthesis that proceeded in a single preparative step. To this end, a solution of ethyl β-aminocrotonate **1** and but-3-yn-2-one **2a** in toluene was stirred at 50 °C for 5.5 h in the presence of acetic acid, or heated at reflux in the presence of zinc(II) bromide, conditions that had promoted the cyclodehydration of dienone intermediate **3a**. Under both sets of conditions, pyridine **4a** was formed in a single preparative step; the reaction catalysed by acetic acid and zinc(II) bromide generating the product in 77 and 65% yield, respectively. An excess of the volatile butynone **3a** (2.4 equivalents) was essential for optimising the yield of the one-pot transformations. Since no aminoheptadienone intermediate **3a** had been isolated from any of these reactions, we concluded that, in the presence of an acid catalyst, cyclodehydration occurred spontaneously under the reaction conditions. The success of these two reactions confirmed that the Bohlmann–Rahtz reaction could be catalysed by either a Brønsted or Lewis acid, affected at a lower cyclodehydration temperature and conducted in a single preparative step.

In order to examine the use of a less volatile alkynone in this reaction, 1-phenylprop-2-yn-1-one **2b** was generated by the oxidation of 1-phenylprop-2-yn-1-ol with *o*-iodoxybenzoic acid (IBX)[11–13] and reacted with ethyl β-aminocrotonate **1** by the traditional two-step procedure[3] and both of our new one-step acid-catalysed methods (Scheme 3). All three reactions gave the



Scheme 3 *Reagents*: A, EtOH, 50 °C, 5 h; then 140–160 °C; B, toluene–AcOH (5 : 1), 50 °C, 5.5 h; C, $ZnBr_2$ (15 mol%), toluene, reflux, 5.5 h.

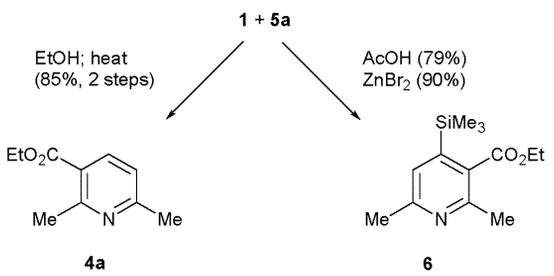
desired product **4b** in excellent yield, the least efficient route being the traditional two-step procedure (Table 3). The zinc(II) bromide catalysed process generated pyridine **4b** in 86% yield after 5.5 hours at a lower reaction temperature, highlighting the advantage of our new procedures over existing methodology.

In these initial studies it was apparent that the one-step reaction using but-3-yn-2-one **2a**, although more convenient, was still not as efficient as the traditional Bohlmann–Rahtz method for this transformation. In a second study of the Bohlmann–Rahtz heteroannulation reaction that used a less volatile alkynone, the experiments were repeated using 4-(trimethylsilyl)but-3-yn-2-one **5a**. One-pot reactions in the presence of acetic acid or zinc(II) bromide gave pyridine **6** in 79 or 90% yield, respectively (Scheme 4). It was noteworthy that, under these conditions, desilylation did not occur during the course of the reaction. In contrast, the traditional Bohlmann–Rahtz annulation generated pyridine **4a** in 85% yield over two steps.

Table 4 The effect of different Lewis acids on the one-pot heteroannulation reaction

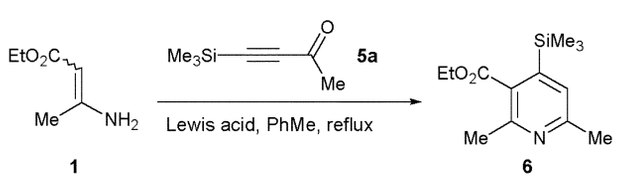
Lewis acid	Catalyst (mol%)	Reaction time (*t*/h)	Yield (%)[a]
None	—	18	0[a]
$ZnBr_2$	10	18	53
$ZnBr_2$	15	5	90
$ZnBr_2$	15	18	68
$ZnBr_2$	20	5	71
$ZnBr_2$	20	18	82
$ZnBr_2$	30	5	59
$ZnBr_2$	40	5	66
$ZnBr_2$	50	5	57
$ZnBr_2$	100	5	44
$ZnCl_2$	20	18	44
$ZnCl_2$	100	18	42
ZnI_2	20	18	66
ZnI_2	100	18	35
$Sc(OTf)_3$	20	18	60
$Tb(OTf)_3$	20	18	45
$Tb(OTf)_3$	100	18	75
$Yb(OTf)_3$	20	18	90
$Yb(OTf)_3$	100	18	70

[a] Isolated yield of pyridine **6** after column chromatography. [b] Only unreacted starting material **1** was isolated.



Scheme 4 Bohlmann–Rahtz annulation reaction using ethyl β-aminocrotonate **1** and 4-(trimethylsilyl)but-3-yn-2-one **5a**.

In order to establish whether any other Lewis acids were capable of promoting this one-pot heteroannulation reaction, a solution of ethyl β-aminocrotonate **1** and 4-(trimethylsilyl)but-3-yn-2-one **5a** in toluene was heated at reflux overnight in the presence of 10–100 mol% of a variety of Lewis acid catalysts (Scheme 5). No reaction occurred in the absence of a Lewis acid

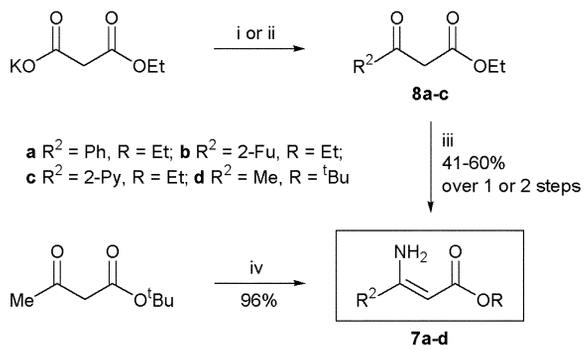


Scheme 5 The Lewis acid catalysed Bohlmann–Rahtz reaction.

catalyst, but in all of the other experiments pyridine **6** was formed, indicating that Lewis acids promote both Michael addition and subsequent spontaneous cyclodehydration. Pyridine **4a** could not be isolated from any of the reactions, confirming that the trimethylsilyl moiety was stable under Lewis acid catalysed conditions. The efficiency of reaction varied considerably depending upon the type and quantity of Lewis acid that was used and the reaction time (Table 4). Only ytterbium(III) trifluoromethanesulfonate gave pyridine **6** in a yield that compared well with zinc(II) bromide, which seemed to give optimum yields when used in 15–20 mol% depending upon the reaction time.

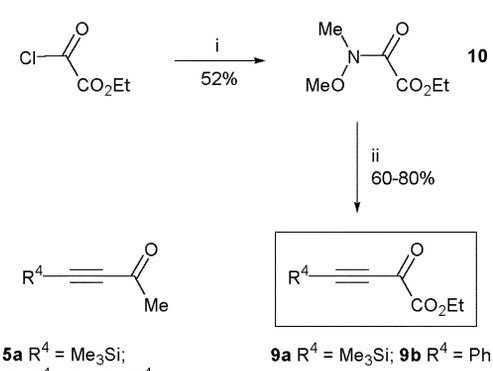
With the success of this facile one-step annulation reaction firmly established, it remained to investigate the scope and versatility of the acetic acid and Lewis acid catalysed methods. To this end, a range of enamino esters were prepared and reacted with a number of different alkynones using the new conditions.

β-Ketoesters **8a–c** were prepared by the homologation of the corresponding acid chloride or mixed anhydride by reaction with magnesium ethyl malonate,[14] generated from potassium ethyl malonate by treatment with methyl magnesium iodide (Scheme 6). The formation of the required enamino ester was



Scheme 6 Preparation of enamines **7a–d**. *Reagents*: i, MeMgI, THF then 2-picolinic acid, EtO_2CCl, THF; ii, MeMgI, THF then 2-furoyl chloride; iii, NH_4OAc, toluene or benzene–AcOH (5 : 1), reflux; iv, aq NH_3.

facilitated by reaction with ammonium acetate–acetic acid in toluene[15,6] to give **7a**, **7b** and **7c** in 60, 41 or 55% overall yield, respectively. In the case of *tert*-butyl acetoacetate, reaction with 35% aqueous ammonia in methanol was found to give superior results,[16] generating enamino ester **7d** in 96% yield. Ethyl 2-oxo-4-(trimethylsilyl)- and ethyl 2-oxo-4-phenylbut-3-ynoate, **9a** and **9b**, were prepared by the addition of lithium (trimethylsilyl)acetylide or lithium phenylacetylide, respectively, generated from the corresponding alkyne by treatment with *n*-butyllithium, to Weinreb amide **10** according to the procedure of Chiu and Jordan (Scheme 7).[17] The Weinreb amide **10** was in turn generated by the reaction of *N,O*-dimethylhydroxylamine and ethyl oxalyl chloride at 0 °C to provide alkynones **9a** and **9b** in moderate yield. This simple procedure provided us with a library of five alkynones, with commercially available 4-(trimethylsilyl)but-3-yn-2-one **5a**, 4-phenylbut-3-yn-2-one **5b** and hex-3-yn-2-one **5c**, in order to investigate the scope of the acid-catalysed Bohlmann–Rahtz heteroannulation reaction.



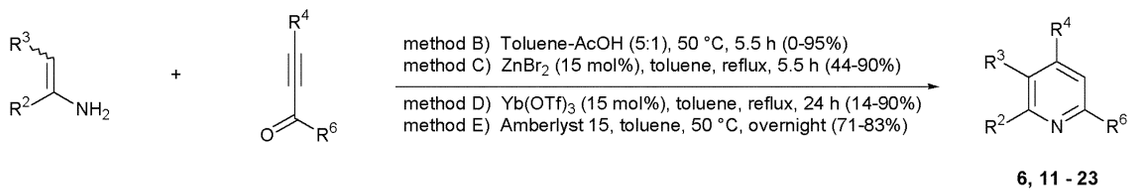
Scheme 7 Preparation of alkynones **9a** and **9b**. *Reagents*: i, Et_3N, MeONHMe·HCl, CH_2Cl_2, 0 °C; ii, PhCCH or Me_3SiCCH, *n*-BuLi, THF, −78 °C; then **10**.

Alkynones **5a–c** and **9a**,**b** were reacted with enamino esters **7a–d** according to one of the new one-step heteroannulation procedures, by heating to 50 °C in toluene–acetic acid for 5.5 h (method B), heating a solution in toluene at reflux in the presence of 15 mol% of zinc(II) bromide for 5 h (method C) or by heating at reflux in the presence of 15 mol% of ytterbium(III) triflate overnight (method D) (Scheme 8). A representative number of reactions was carried out (Table 5) and the different one-step procedures were compared. In almost all of the cases investigated, the desired pyridine was produced in reasonable

Table 5 Comparing the four one-step heteroannulation methods for the synthesis of pyridines **11**–**23**

Enamine	Alkynone	Product	R^2	R^3	R^4	R^6	Method B Yield (%)	Method C Yield (%)	Method D Yield (%)	Method E Yield (%)
1	**5a**	**6**	Me	EtO_2C	Me_3Si	Me	79	90	90	—
1	**5b**	**11**	Me	EtO_2C	Ph	Me	0	—	—	71
1	**5c**	**12**	Me	EtO_2C	Et	Me	85	67	83	—
1	**9a**	**13**	Me	EtO_2C	Me_3Si	CO_2Et	—	44[a]	33	—
1	**9b**	**14**	Me	EtO_2C	Ph	CO_2Et	95	85	55	—
7a	**2a**	**15**	Ph	EtO_2C	H	Me	73	70	58	—
7a	**5b**	**16**	Ph	EtO_2C	Ph	Me	—	62	68	—
7a	**5c**	**17**	Ph	EtO_2C	Et	Me	65	72	32	—
7a	**9b**	**18**	Ph	EtO_2C	Ph	CO_2Et	—	65	44	—
7b	**5a**	**19**	2-Furyl	EtO_2C	Me_3Si	Me	80	—	—	73
7c	**5c**	**20**	2-Pyridyl	EtO_2C	Et	Me	—	62	68	—
7d	**5a**	**21**	Me	$^tBuO_2C$	H	Me	0	—	—	83[b]
7d	**5b**	**22**	Me	$^tBuO_2C$	Ph	Me	—	85	32	76
7d	**5c**	**23**	Me	$^tBuO_2C$	Et	Me	—	70	14	80

[a] Desilylated pyridine (R^4 = H) was also produced. [b] Desilylation occurred during the course of the reaction.



Scheme 8 Examining the scope of the one-step Bohlmann–Rahtz heteroannulation procedure.

yield. Furthermore, it was evident that these new procedures were appropriate for the formation of tetrasubstituted products, the introduction of a range of different substituents at the terminal position of the alkyne seeming not to affect the outcome of these reactions. Out of the two Lewis acid catalysed procedures (C and D), it appeared that in most instances the zinc(II) bromide catalysed method was superior, increasing the efficiency of reaction dramatically in a much shorter time. The use of acetic acid or zinc(II) bromide as catalyst (method B or C) seemed to give similar results in the majority of cases, verifying that both of these procedures were valuable new one-step methods for the facile synthesis of tetrasubstituted pyridines.

In addition, it was decided to explore a new milder method for conjugate addition–cyclodehydration that would be compatible with acid sensitive substrates and that would lend itself well to combinatorial methodology. In this procedure (method E), a solution of the alkynone and enamine in toluene was stirred overnight at 50 °C in the presence of Amberlyst 15 ion exchange resin. Once the reaction was complete, the resin was filtered and washed to give the crude pyridine product directly in good yield, even in reactions that failed or performed poorly using acetic acid as a catalyst. In all cases, this new method compared favourably with other procedures and its simplicity made it a compelling alternative to existing methodology.

New modified conditions for Bohlmann–Rahtz pyridine synthesis were successful using either acetic acid, zinc(II) bromide, ytterbium(III) triflate or an acidic ion exchange resin. The temperature required to affect this heteroannulation reaction has been reduced but, more importantly, these procedures can now be conducted in a single preparative step. With a number of new experimental procedures established, work is now underway to apply these novel methods to the synthesis of heterocyclic natural products to be reported in due course.

Experimental

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Unless otherwise stated, reactions were performed under an atmosphere of dry nitrogen. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm).

Fully characterised compounds were chromatographically homogeneous. Melting points were determined on a Kofler hot stage apparatus. Infra-red spectra were recorded in the range 4000–600 cm^{-1} on a Perkin–Elmer 1600 series FTIR spectrometer using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a Nujol mull, and are reported in cm^{-1}. NMR spectra were recorded using a Bruker DPX 400 instrument operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra; *J* values were recorded in Hz and multiplicities are expressed by the usual conventions. Low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument using electrospray ionization (ES) unless otherwise stated. APcI refers to atmospheric pressure chemical ionization, CI refers to chemical ionization (ammonia) and EI refers to electron ionization. High resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using the ionization methods specified. Microanalyses were recorded using a Perkin–Elmer 240C Elemental Analyzer.

1-Phenylprop-2-yn-1-one 2b

A solution of *o*-iodoxybenzoic acid (IBX) (8.50 g, 30.3 mmol) in DMSO (230 ml) was stirred for 15 min at room temperature until homogeneous. A solution of 1-phenylprop-2-yn-1-ol (1.60 g, 12.1 mmol) in DMSO (5 ml) was added and the mixture was stirred for 5 h. Water (25 ml) was added and the mixture was stirred at room temperature for 10 min, cooled in ice and partitioned between water (200 ml) and ether (150 ml). The mixture was filtered through Celite® and the aqueous layer was further extracted with ether (120 ml). The organic extracts were combined, washed sequentially with water (3 × 120 ml), saturated aqueous sodium hydrogen carbonate solution (160 ml) and brine (160 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (1.56 g, 99%), mp 49–50 °C (methanol) (lit.,[18] mp 47–48 °C) (Found: M^+,

130.0418. C_9H_6O requires *M*, 130.0419); ν_{max}(KBr)/cm^{-1} 3232, 2094, 1644, 1596, 1579, 1452, 1315, 1265, 1176, 1007 and 697; δ_H(400 MHz; $CDCl_3$) 8.10 (2H, m, *o*-Ph*H*), 7.57 (1H, m, *p*-Ph*H*), 7.50 (2H, m, *m*-Ph*H*), 3.38 (1H, s, 3-H); δ_C(100 MHz; $CDCl_3$) 176.4 (C), 135.0 (C), 133.5 (CH), 128.6 (CH), 127.7 (CH), 80.1 (C) and 79.2 (CH); *m*/*z* (EI) 130 (83), 102 (100) and 77 (37).

(4*E*)-2-Amino-3-ethoxycarbonylhepta-2,4-dien-6-one 3a

A solution of ethyl β-aminocrotonate **1** (0.2 ml, 1.6 mmol) and but-3-yn-2-one **2a** (0.3 ml, 3.8 mmol) or 4-trimethylsilylbut-3-yn-2-one **5** (0.52 ml, 3.2 mmol) in ethanol (5 ml) was stirred at 50 °C for 5 h, cooled and then evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 1), gave the *title compound* as a yellow solid (0.28 g, 98%); mp 125.5–126.4 °C (light petroleum) (lit.,[3] mp 135 °C) (Found: C, 60.9; H, 7.6; N, 7.1. Calc. for $C_{10}H_{15}NO_3$: C, 60.5; H, 7.6; N, 7.0%) (Found: MH$^+$, 198.1130. $C_{10}H_{15}NO_3$ requires *M*H, 198.1129); ν_{max}(Nujol)/cm^{-1} 3335, 3194, 2924, 1643, 1548 and 1462; δ_H(400 MHz; $CDCl_3$) 9.59 (1 H, br s, NH), 7.53 (1 H, d, *J* 15.5, 4-H), 6.50 (1 H, d, *J* 15.5, 5-H), 5.57 (1 H, br s, NH), 4.20 (2 H, q, *J* 7.1, C*H*$_2$Me), 2.23 (3 H, s, Me), 2.17 (3 H, s, Me), 1.31 (3 H, t, *J* 7.1, CH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 199.7 (C), 170.5 (C), 166.5 (C), 140.4 (CH), 122.0 (CH), 95.3 (C), 59.9 (CH_2), 29.2 (Me), 23.5 (Me) and 15.3 (Me); *m*/*z* (APcI) 198 (MH$^+$, 9%), 181 (100), 152 (29) and 107 (9).

Cyclodehydration procedure catalysed by acetic acid

A solution of (4*E*)-2-amino-3-ethoxycarbonylhepta-2,4-dien-6-one **3a** (0.10 g, 0.56 mmol) in toluene–glacial acetic acid (6 ml) was stirred at room temperature for 2.5 h and then heated to 50 °C for 1 h in a flask fitted with a drying tube. The solution was allowed to cool and partitioned between saturated aqueous sodium hydrogen carbonate solution (25 ml) and ethyl acetate (25 ml). The aqueous layer was further extracted with ethyl acetate (2 × 15 ml) and the organic extracts were combined, washed with brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give ethyl 2,6-dimethylpyridine-3-carboxylate **4a** as a brown oil (0.10 g, quantitative).

Cyclodehydration procedure catalysed by zinc(II) bromide

A solution of (4*E*)-2-amino-3-ethoxycarbonylhepta-2,4-dien-6-one **3a** (0.10 g, 0.56 mmol) and zinc(II) bromide (20 mg, 0.08 mmol) in toluene (6 ml) was heated at reflux for 5 h, allowed to cool and then water (6 ml) was added. The mixture was stirred for 10 min and extracted with ethyl acetate (3 × 10 ml). The organic extracts were combined, washed with brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give ethyl 2,6-dimethylpyridine-3-carboxylate **4a** as a brown oil (0.10 g, quantitative).

General procedure for the traditional two-step Bohlmann–Rahtz reaction (method A)[3]

A solution of ethyl β-aminocrotonate **1** (~1 mmol, 1 equiv.) and alkynone (2.4 equiv.) in ethanol (5 ml) was stirred at 50 °C for 5 h, cooled and then evaporated *in vacuo* to give dienone intermediate **3** as a yellow solid. The residue was heated at 140–160 °C in a flask fitted with a drying tube for 1–2 h and allowed to cool to give pyridine **4**.

General procedure for the one-step Bohlmann–Rahtz reaction catalysed by acetic acid (method B)

A solution of the enamine (~1 mmol, 1 equiv.) and alkynone (1.2–2.4 equiv.) in toluene–glacial acetic acid (5 : 1) (5 ml) was stirred at 50 °C for 6 h. The mixture was partitioned between toluene (30 ml) and saturated aqueous sodium hydrogen carbonate solution (30 ml), the aqueous layer was further extracted with toluene (2 × 20 ml) and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the pyridine product.

General procedure for the one-step Bohlmann–Rahtz reaction catalysed by zinc(II) bromide (method C)

A solution of the enamine (~1 mmol, 1 equiv.), alkynone (1.2 equiv.) and zinc(II) bromide (15–20 mol%) in toluene (6 ml) was heated at reflux for 6 h, allowed to cool, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (6 ml) and brine (6 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the pyridine product.

General procedure for the one-step Bohlmann–Rahtz reaction catalysed by ytterbium(III) triflate (method D)

A solution of the enamine (~1 mmol, 1 equiv.), alkynone (1.2 equiv.) and ytterbium(III) triflate (15–20 mol%) in toluene (6 ml) was heated at reflux for 16 h, allowed to cool and water (6 ml) was added. The mixture was heated at reflux for 20 min and extracted with ethyl acetate (2 × 10 ml). The organic layers were combined, washed with brine (6 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the pyridine product.

General procedure for the one-step Bohlmann–Rahtz reaction catalysed by Amberlyst 15 ion exchange resin (method E)

A solution of the enamine (~1 mmol, 1 equiv.), alkynone (1.2 equiv.) and Amberlyst 15 ion exchange resin (0.1 g) in toluene (4 ml) was stirred at 50 °C for 26 h. The mixture was filtered, the resin was washed with chloroform (5 ml) and the filtrate was evaporated *in vacuo* to give the pyridine product.

Ethyl 2,6-dimethylpyridine-3-carboxylate 4a

Ethyl β-aminocrotonate **1** (0.13 g, 1.0 mmol) and but-3-yn-2-one **2a** (0.16 g, 2.4 mmol) were reacted according to the two- or one-step general procedure (method A or B). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (Found: MH$^+$, 180.1024. $C_{10}H_{13}NO_2$ requires *M*H, 180.1021); ν_{max}(film)/cm^{-1} 2983, 1724, 1593, 1446 and 772; δ_H(400 MHz; $CDCl_3$) 8.03 (1 H, d, *J* 8.0, 4-H), 6.99 (1 H, d, *J* 8.0, 5-H), 4.29 (2 H, q, *J* 7.1, CH_2), 2.74 (3 H, s, 6-Me), 2.50 (3 H, s, 2-Me), 1.32 (3 H, t, *J* 7.1, Me); δ_C(100 MHz; $CDCl_3$) 167.1 (C), 161.6 (C), 159.8 (C), 139.2 (CH), 123.1 (C), 120.8 (CH), 61.4 (CH_2), 25.2 (Me), 25.1 (Me) and 14.7 (Me); *m*/*z* (APcI) 180 (MH$^+$, 100%).

Ethyl 2-methyl-6-phenylpyridine-3-carboxylate 4b

Ethyl β-aminocrotonate **1** (0.13 g, 1.0 mmol) and 1-phenylprop-2-yn-1-one **2b** (0.16 g, 1.2 mmol) were reacted according to the two- or one-step general procedure (method A, B or C). Purification by flash chromatography on silica, eluting with dichloromethane–light petroleum (1 : 1), gave the *title compound*[19] as a pale yellow solid, mp 44–45 °C (methanol) (lit.,[3] mp 44 °C) (Found: MH$^+$, 242.1182. $C_{15}H_{15}NO_2$ requires *M*H, 242.1182); ν_{max}(KBr)/cm^{-1} 2980, 2925, 2890, 1717, 1581, 1476, 1277, 1090 and 1022; δ_H(400 MHz; $CDCl_3$) 8.19 (1 H, d, *J* 8.2, 4-H), 8.00 (2 H, m, *o*-Ph*H*), 7.55 (1 H, d, *J* 8.2, 5-H), 7.41 (3 H, m, *m*,*p*-Ph*H*), 4.33 (2 H, q, *J* 7.1, CH_2), 2.85 (3 H, s, 2-Me), 1.35 (3 H, t, *J* 7.1, Me); δ_C(100 MHz; $CDCl_3$) 165.7 (C), 159.1 (C), 158.1 (C), 138.5 (CH), 137.6 (C), 128.7 (CH), 128.0 (CH), 126.5 (CH), 122.8 (C), 116.5 (CH), 60.3 (CH_2), 24.6 (Me) and 13.5 (Me); *m*/*z* (APcI) 241 (M$^+$, 91%), 240 (69), 212 (32), 196 (100), 195 (98), 168 (43) and 167 (40).

Ethyl 2,6-dimethyl-4-(trimethylsilyl)pyridine-3-carboxylate 6

Ethyl β-aminocrotonate **1** (0.1 g, 0.79 mmol) and 4-(trimethylsilyl)but-3-yn-2-one **5a** (0.17 ml, 1.0 mmol) were reacted

according to the one-step general procedure (method B, C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (0.16 g, 79%) (Found: MH^+, 252.1420. $C_{13}H_{21}NO_2Si$ requires *M*H, 252.1420); ν_{max}(film)/cm^{-1} 2956, 2903, 1724, 1529, 1104, 1085 and 1016; δ_H(400 MHz; $CDCl_3$) 7.12 (1 H, s, Py*H*), 4.35 (2 H, q, *J* 7.2, C*H*$_2$Me), 2.54 (3 H, s, Me), 2.51 (3 H, s, Me), 1.37 (3 H, t, *J* 7.2, CH$_2$*Me*), 0.26 (9 H, s, $SiMe_3$); δ_C(100 MHz; $CDCl_3$) 171.1 (C), 158.5 (C), 154.9 (C), 149.4 (C), 131.5 (C), 126.6 (CH), 62.1 (CH_2), 30.5 (Me), 24.1 (Me) 14.9 (Me) and 0.0 (Me); *m*/*z* (APcI) 252 (MH^+, 100%) and 236 (2).

Ethyl 3-amino-3-phenylpropenoate 7a

A solution of ethyl benzoylacetate **8a** (5 ml, 29.0 mmol) and ammonium acetate (13.4 g, 0.17 mol) was heated at reflux in toluene–glacial acetic acid (5 : 1) (40 ml) for 20 h. The mixture was partitioned between water (100 ml) and diethyl ether (60 ml), the aqueous layer was further extracted with diethyl ether (2 × 25 ml) and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (50 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (3.32 g, 60%) (Found: MH^+, 192.1024. $C_{11}H_{13}NO_2$, requires *M*H, 192.1025); ν_{max}(film)/cm^{-1} 3440, 3326, 3066, 2979, 1663, 1556, 796, 772 and 699; δ_H(400 MHz; $CDCl_3$) 8.50–6.50 (1 H, br s, NH), 7.48 (2 H, m, *o*-Ph*H*), 7.35 (3 H, m, *m,p*-Ph*H*), 6.1–3.8 (1 H, br s, NH), 4.90, (1 H, s, CH), 4.11 (2 H, q, *J* 7.1, CH_2), 1.23 (3 H, t, *J* 7.1, Me); δ_C(100 MHz, $CDCl_3$) 170.9 (C), 160.9 (C), 138.1 (C), 130.7 (CH), 129.3 (CH), 126.6 (CH), 85.0 (CH), 59.4 (CH_2) and 15.0 (Me); *m*/*z* (APcI) 192 (MH^+, 100%), 186 (36) and 103 (11).

Ethyl 3-amino-3-(2-furyl)propenoate 7b

A solution of ethyl 3-(2-furyl)-3-oxopropanoate **8b** (1.17 g, 6.44 mmol) and ammonium acetate (3.9 g, 50.6 mmol) was heated at reflux in benzene–glacial acetic acid (5 : 1) (25 ml) for 25 h. The mixture was partitioned between saturated aqueous sodium hydrogen carbonate solution (50 ml) and diethyl ether (50 ml), the aqueous layer was further extracted with diethyl ether (2 × 20 ml) and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a dark oil (0.82 g, 70%) (Found: MH^+, 182.0814. $C_9H_{11}NO_3$ requires *M*H, 182.0817); ν_{max}(film)/cm^{-1} 3446, 3334, 3125, 2980, 1662, 1544, 790 and 751; δ_H(400 MHz; $CDCl_3$) 7.42 (1 H, m, Fu*H*), 6.69 (1 H, m, Fu*H*), 7.20–5.55 (2 H, br s, NH_2), 6.41 (1 H, m, Fu*H*), 5.07 (1 H, s, CH), 4.10 (2 H, q, *J* 7.2, CH_2), 1.22, (3 H, t, *J* 7.2, Me); δ_C(100 MHz; $CDCl_3$) 170.9 (C), 149.7 (C), 149.2 (C), 144.1 (CH), 112.5 (CH), 109.8 (CH), 81.7 (CH), 59.4 (CH_2) and 15.0 (Me); *m*/*z* (APcI) 182 (MH^+, 100%), 117 (18), 107 (11) and 59 (2).

Ethyl 3-amino-3-(2-pyridyl)propenoate 7c

A solution of methylmagnesium iodide in THF (3 M; 5.3 ml, 16 mmol) was added dropwise over 10 min to a stirred suspension of ethyl potassium malonate (2.91 g, 16.51 mmol) in dry THF (35 ml) at 0 °C. The mixture was stirred for 30 min, warmed to room temperature and stirred for a further 2 h to give a solution of the magnesium enolate of ethyl hydrogen malonate in THF. Ethyl chloroformate (0.8 ml, 8.37 mmol) was added dropwise over 5 min to a solution of picolinic acid (1.08 g, 8.78 mmol) and triethylamine (1.2 ml, 8.61 mmol) in dry THF at 0 °C. The mixture was stirred for 30 min and added to the solution of the magnesium enolate of ethyl hydrogen malonate in THF. The reaction mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution (25 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned between water (25 ml) and chloroform (75 ml), the aqueous layer was further extracted with chloroform (2 × 30 ml) and the combined organic extracts were washed sequentially with glacial acetic acid (5%; 50 ml), saturated aqueous sodium hydrogen carbonate solution (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a dark oil (1.0 g). Ammonium acetate (4.1 g, 53.19 mmol) and toluene–glacial acetic acid (5 : 1) (50 ml) were added and the solution was heated at reflux for 20 h, allowed to cool and partitioned between saturated aqueous sodium hydrogen carbonate solution (100 ml) and ethyl acetate (50 ml). The aqueous phase was further extracted with ethyl acetate (2 × 50 ml) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (40 ml) and brine (40 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a colourless oil (0.84 g, 50%) (Found: MH^+, 193.0977. $C_{10}H_{12}N_2O_2$, requires *M*H, 193.0977); ν_{max}(film)/cm^{-1} 3462, 3333, 2980, 1665, 1613, 1545, 1465, 1363, 1312, 1189, 1152, 1096, 1051, 996, 782 and 751; δ_H(400 MHz; $CDCl_3$) 8.55 (1 H, m, Py*H*), 8.2–7.6 (1 H, br s, NH), 7.66 (2 H, m, Py*H*), 7.26 (1 H, m, Py*H*), 6.80 (1 H, br s, NH), 5.26 (1 H, s, CH), 4.14 (2 H, q, *J* 7.2, CH_2), 1.24 (3 H, t, *J* 7.2, Me); δ_C(100 MHz; $CDCl_3$) 171.0 (C), 155.9 (C), 151.7 (C), 149.2 (CH), 137.2 (CH), 125.1 (CH), 120.6 (CH), 82.6 (CH), 59.4 (CH_2) and 15.0 (Me); *m*/*z* (EI) 192 (M^+, 37%), 147 (59), 120 (100), 105 (87) and 79 (82).

tert-Butyl β-aminocrotonate 7d

According to a modified literature procedure,[16] a solution of *tert*-butyl acetoacetate (2 ml, 1.21 mmol) and aqueous ammonium hydroxide solution (35%; 20 ml) in methanol (20 ml) was stirred overnight. The solution was concentrated *in vacuo* and partitioned between water (20 ml) and ethyl acetate (20 ml). The aqueous layer was further extracted with ethyl acetate (3 × 30 ml) and the combined organic layers were washed with brine (15 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound*[16] as a pale yellow oil (0.18 g, 96%) (Found: MH^+, 158.1183. $C_8H_{15}NO_2$ requires *M*H, 158.1181); ν_{max}(film)/cm^{-1} 3448, 3334, 2977, 2925, 1655, 1620, 1565, 1451, 1365, 1298, 1149, 983, 790 and 757; δ_H(400 MHz; $CDCl_3$) 7.78 (1 H, br s, NH), 4.43 (1 H, s, CH), 4.39 (1 H, br s, NH), 1.80 (3 H, s, Me), 1.40 (9H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 170.6 (C), 159.3 (C), 86.2 (CH), 78.5 (C), 29.0 (Me) and 22.7 (Me); *m*/*z* (EI) 157 (M^+, 11%), 101 (53), 83 (100), 57 (35) and 41 (82).

Ethyl 3-(2-furyl)-3-oxopropanoate 8b

A solution of methylmagnesium iodide (3 M; 5.79 ml, 17 mmol) was added dropwise over 15 min to a stirred suspension of ethyl potassium malonate (2.95 g, 17 mmol) in dry THF (40 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, warmed to room temperature and stirred for a further 2.5 h. 2-Furoyl chloride (1.10 ml, 0.011 mol) was added dropwise over 10 min and the solution was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution (25 ml) was added, the mixture was concentrated *in vacuo* and partitioned between chloroform (75 ml) and water (75 ml). The aqueous layer was further extracted with chloroform (2 × 25 ml) and the combined organic layers were washed sequentially with acetic acid (5%) (25 ml), saturated aqueous sodium hydrogen carbonate solution (25 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a colourless oil (1.80 g, 58%) (Found: MH^+,

183.0657. $C_9H_{10}O_4$ requires *M*H, 183.0658); ν_{max}(film)/cm^{-1} 3135, 2983, 1739, 1677, 1571, 1468, 1393, 1155, 1084, 1027, 915, 884 and 769; δ_H(400 MHz; $CDCl_3$) 7.55 (1 H, d, *J* 0.8, Fu*H*), 7.20 (1 H, t, *J* 3.7, Fu*H*), 6.51 (1 H, m, Fu*H*), 4.14 (2 H, q, *J* 7.2, C*H*$_2$Me), 3.78 (2 H, s, CH_2), 1.19 (3 H, t, *J* 7.2, Me). δ_C(100 MHz; $CDCl_3$) 181.5 (C), 167.4 (C), 152.4 (C), 147.5 (CH), 118.8 (CH), 113.1 (CH), 61.9 (CH_2), 45.9 (CH_2) and 14.5 (Me); *m*/*z* (EI) 182 (M^+, 15%) and 95 (100).

Ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate 9a

A solution of *n*-butyllithium in hexanes (2.5 M; 2.36 ml, 5.9 mmol) was added dropwise over 10 min to a stirred solution of (trimethylsilyl)acetylene (1.2 ml, 8.5 mmol) in dry THF (10 ml) at −78 °C. The solution was stirred for 30 min and added dropwise to a solution of monoethyloxalic acid *N*-methoxy-*N*-methylamide **10** (0.64 g, 4.0 mmol) in dry THF (10 ml) at −78 °C. The mixture was stirred for 1 h, warmed to 0 °C and stirred for a further 2 h. The solution was poured over ice (30 g), concentrated *in vacuo* and partitioned between phosphoric acid (20%; 60 ml) and diethyl ether (120 ml). The aqueous layer was further extracted with diethyl ether (2 × 40 ml) and the combined organic extracts were washed sequentially with phosphoric acid (10%; 30 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–diethyl ether (9 : 1) gave the *title compound* as a dark oil (1.01 g, 60%) (Found: MNH_4^+, 216.1056. $C_9H_{14}O_3Si$ requires *M*NH_4, 216.1057); ν_{max}(film)/cm^{-1} 2984, 2904, 2149, 1742, 1686, 1447, 1370, 1254, 1101, 1014, 847, 763 and 716; δ_H(400 MHz; $CDCl_3$) 4.13 (2 H, q, *J* 7.1, C*H*$_2$Me), 1.15 (3 H, t, *J* 7.1, CH_2*Me*), 0.06 (9 H, s, $SiMe_3$); δ_C(100 MHz; $CDCl_3$) 170.3 (C), 160.0 (C), 107.8 (C), 101.2 (C), 64.3 (CH_2), 14.9 (Me) and 0.0 (Me); *m*/*z* (CI) 216 (MNH_4^+, 100%), 123 (19), 96 (13), 90 (42), 52 (64).

Ethyl 2-oxo-4-phenylbut-3-ynoate 9b[17]

A solution of *n*-butyllithium in hexanes (2.5 M; 2.48 ml, 6.2 mmol) was added dropwise over 10 min to a stirred solution of phenylacetylene (0.68 ml, 6.2 mmol) in dry THF (15 ml) at −78 °C. The solution was stirred for 35 min and added dropwise to a solution of monoethyloxalic acid *N*-methoxy-*N*-methylamide **10** (1.00 g, 6.21 mmol) in dry THF (30 ml) at −78 °C. The mixture was stirred for 20 min, poured over ice (10 g), and partitioned between phosphoric acid (20%; 30 ml) and diethyl ether (30 ml). The aqueous layer was further extracted with diethyl ether (2 × 25 ml) and the combined organic extracts were washed sequentially with phosphoric acid (10%; 25 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (6 : 1) gave the *title compound* as a yellow oil (1.0 g, 80%) (Found: MNH_4^+, 220.0974. $C_{12}H_{10}O_3$ requires *M*NH_4, 220.0967); ν_{max}(film)/cm^{-1} 2985, 2204, 1738, 1678, 858, 761 and 688; δ_H(400 MHz; $CDCl_3$) 7.60 (2 H, *J* 7.0, d, *o*-Ph*H*), 7.45 (1 H, m, *p*-Ph*H*), 7.35 (2 H, m, *m*-Ph*H*), 4.34 (2 H, q, *J* 7.2, CH_2), 1.35 (3 H, t, *J* 7.2, Me); δ_C(100 MHz; $CDCl_3$) 170.0 (C), 159.6 (C), 134.2 (CH), 132.3 (CH), 129.2 (CH), 119.4 (C), 98.5 (C), 87.6 (C), 63.7 (CH_2) and 14.4 (Me); *m*/*z* (CI) 203 (MH^+, 6%), 176 (8), 175 (100), 105 (22) and 105 (58).

Monoethyloxalic acid-*N*-methoxy-*N*-methylamide 10[17]

Triethylamine (5.0 ml, 35.9 mmol) was added over 10 min to a solution of *N,O*-dimethylhydroxlamine hydrochloride (1.76 g, 19.9 mmol) and ethyl oxalyl chloride (2 ml, 18.05 mmol) in dry DCM (30 ml) at 0 °C and the mixture was stirred for 40 min. Methanol (5 ml, 0.12 M) was added and the mixture was evaporated *in vacuo*. Tetrahydrofuran (20 ml) was added and the precipitate was filtered under suction, washing with THF (2 × 10 ml). The filtrate was evaporated *in vacuo* and distilled to give the *title compound* as a colourless oil (1.54 g, 53%), bp 55–60 °C (10 mmHg) (Found: MH^+, 162.0766. $C_6H_{11}NO_4$, requires *M*H, 162.0761); ν_{max}(film)/cm^{-1} 2985, 2943, 1747 and 1682; δ_H(400 MHz; $CDCl_3$) 4.28 (2 H, *J* 7.1, q, CH_2), 3.69 (3 H, s, Me), 3.17 (3 H, s, Me), 1.30 (3 H, *J* 7.1, t, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 162.8 (C), 162.4 (C), 62.7 (Me), 62.5 (Me), 31.8 (CH_2) and 14.4 (Me); *m*/*z* (APcI) 162 (MH^+, 100%), 134 (14), 106 (52), 88 (92) and 83 (50).

Ethyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate 11

Ethyl β-aminocrotonate **1** (0.1 ml, 0.79 mmol) and 4-phenylbut-3-yn-2-one **5b** (0.15 ml, 1.03 mmol) were reacted according to the one-step general procedure (method E). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (0.14 g, 71%) (Found: MH^+, 256.1337. $C_{16}H_{17}NO_2$ requires *M*H, 256.1334); ν_{max}(film)/cm^{-1} 2978, 2926, 1725, 1587, 1548, 1266, 1206, 1083, 870, 767 and 701; δ_H(400 MHz; $CDCl_3$) 7.30 (5 H, m, Ph*H*), 6.94 (1 H, s, Py*H*), 4.01 (2 H, q, *J* 7.1, CH_2), 2.54 (3 H, s, Me), 2.50 (3 H, s, Me), 0.90 (3 H, t, *J* 7.1, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 169.5 (C), 159.1 (C), 155.5 (C), 148.9 (C), 139.2 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 126.1 (C), 121.6 (CH), 61.7 (CH_2), 24.9 (Me), 23.2 (Me) and 14.0 (Me); *m*/*z* (APcI) 256 (MH^+, 100%) and 252 (2).

Ethyl 2,6-dimethyl-4-ethylpyridine-3-carboxylate 12

Ethyl β-aminocrotonate **1** (0.1 ml, 0.79 mmol) and hex-3-yn-2-one **5c** (0.1 ml, 0.92 mmol) were reacted according to the one-step general procedure (method B, C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (Found: MH^+, 208.1337. $C_{12}H_{17}NO_2$ requires *M*H, 208.1335); δ_{max}(film)/cm^{-1} 2975, 2937, 1726, 1595, 1561, 1190 and 1089; δ_H(400MHz; $CDCl_3$) 6.85 (1 H, s, Py*H*), 4.32 (2 H, q, *J* 7.1, OC*H*$_2$Me), 2.50 (2 H, q, *J* 7.6, C*H*$_2$Me), 2.44 (3 H, s, Me), 2.42 (3 H, s, Me), 1.30 (3 H, t, *J* 7.1, CH_2*Me*), 1.12 (3 H, t, *J* 7.6, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 169.5 (C), 158.9 (C), 154.7 (C), 151.1 (C), 126.7 (C), 120.7 (CH), 61.6 (CH_2), 26.6 (CH_2), 24.7 (Me), 23.2 (Me), 15.0 (Me) and 14.5 (Me); *m*/*z* (APcI) 208 (MH^+, 100%).

Diethyl 2-methyl-4-(trimethylsilyl)pyridine-3,6-dicarboxylate 13

Ethyl β-aminocrotonate **1** (0.1 g, 0.79 mmol) and ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate **9a** (0.2 g, 1.01 mmol) were reacted according to the one-step general procedure (method C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a dark oil (Found: MH^+, 310.1474. $C_{15}H_{23}NO_4Si$ requires *M*H, 310.1473); ν_{max}(film)/cm^{-1} 2982, 1724, 1531, 1447, 1269, 1153, 1026, 955, 847 and 759; δ_H(400 MHz; $CDCl_3$) 7.94 (1 H, s, Py*H*), 4.31 (2 H, q, *J* 7.1, CH_2), 4.24 (2 H, q, *J* 7.1, CH_2), 2.50 (3 H, s, Me), 1.28 (6 H, app t, *J* 7.1, Me), 0.17 (9 H, s, $SiMe_3$); δ_C(100 MHz; $CDCl_3$) 170.5 (C), 166.3 (C), 155.9 (C),150.6 (C), 147.8 (C), 138.0 (C), 128.4 (CH), 63.1 (CH_2), 62.8 (CH_2), 24.3 (Me), 15.3 (Me), 15.1 (Me) and 0.0 (Me); *m*/*z* (APcI) 310 (MH^+, 100%).

Diethyl 2-methyl-4-phenylpyridine-3,6-dicarboxylate 14

Ethyl β-aminocrotonate **1** (0.1 ml, 0.79 mmol) and ethyl 2-oxo-4-phenylbut-3-ynoate **9b** (0.21 g, 1.29 mmol) were reacted according to the one-step general procedure (method B, C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (85 : 15), gave the *title compound* as a colourless solid, mp 85–86 °C (light petroleum) (Found: C, 69.0; H, 6.1; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 69.4; H, 6.3; N, 4.6%) (Found: MH^+, 314.1392. $C_{18}H_{19}NO_4$ requires *M*H, 314.1388); ν_{max}(Nujol)/cm^{-1} 2982, 1730, 1582, 1552, 1148, 1081

and 1024; δ_H(400 MHz; $CDCl_3$) 7.93 (1 H, s, Py*H*), 7.36 (5 H, m, Ph*H*), 4.42 (2 H, q, *J* 7.1, CH_2), 4.08 (2 H, q, *J* 7.1, CH_2), 2.65 (3 H, s, Me), 1.36 (3 H, t, *J* 7.1, CH_2*Me*), 0.95 (3 H, t, *J* 7.1, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 168.6 (C), 165.2 (C), 156.6 (C), 149.4 (C), 148.3 (C), 138.0 (C), 131.7 (C), 129.4 (CH), 129.1 (CH), 128.4 (CH), 123.7 (CH), 62.6 (CH_2), 62.2 (CH_2), 23.5 (Me), 14.7 (Me) and 14.1 (Me); *m*/*z* (APcI) 314 (MH^+, 100%) and 268 (1).

Ethyl 6-methyl-2-phenylpyridine-3-carboxylate 15

Ethyl 3-amino-3-phenylpropenoate **7a** (0.11 ml, 0.58 mmol) and but-3-yn-2-one **2a** (0.06 ml, 0.77 mmol) were reacted according to the one-step general procedure (method B, C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the title compound as a pale yellow oil (Found: MH^+, 242.1181. $C_{15}H_{15}NO_2$ requires *M*H, 242.1181); ν_{max}(film)/cm^{-1} 2981, 2926, 1718, 1589, 1137, 1052, 838 and 766; δ_H(400 MHz; $CDCl_3$) 7.93 (1 H, d, *J* 8.0, Py*H*), 7.37 (5 H, m, PhH), 7.10 (1 H, d, *J* 8.0, Py*H*), 4.03 (2 H, q, *J* 7.2, CH_2), 2.56 (3 H, s, Me), 0.94 (3 H, t, *J* 7.2, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 168.6 (C), 161.2 (C), 159.1 (C), 141.0 (C), 138.7 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 124.8 (C), 121.6 (CH), 61.7 (CH_2), 27.8 (Me) and 14.0 (Me); *m*/*z* (APcI) 242 (MH^+, 100%) and 214 (1).

Ethyl 2,4-diphenyl-6-methylpyridine-3-carboxylate 16

Ethyl 3-amino-3-phenylpropenoate **7a** (0.1 g, 0.63 mmol) and 4-phenylbut-3-yn-2-one **5b** (0.11 ml, 0.76 mmol) were reacted according to the one-step general procedure (method C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a colourless solid, mp 99–100 °C (light petroleum) (Found: C, 79.5; H, 6.0; N, 4.4. $C_{21}H_{19}NO_2$ requires C, 79.9; H, 6.3; N, 4.4%) (Found: MH^+, 318.1494. $C_{21}H_{19}NO_2$ requires *M*H, 318.1496); ν_{max}(Nujol)/cm^{-1} 2928, 1722, 1543, 1269, 1205, 1110, 1053, 770, 746 and 701; δ_H(400 MHz; $CDCl_3$) 7.53 (2 H, m, Ph*H*), 7.30 (8 H, m, Ph*H*), 7.07 (1 H, s, PyH), 3.83 (2 H, q, *J* 7.2, CH_2), 2.57 (3 H, s, Me), 0.75 (3 H, t, *J* 7.2, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 169.7 (C), 157.9 (C), 155.5 (C), 147.8 (C), 138.9 (C), 137.3 (C), 127.5 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 124.9 (C), 121.2 (CH), 60.2 (CH_2), 23.6 (Me) and 12.4 (Me); *m*/*z* (APcI) 319 (MH^+, 100%), 305 (1) and 263 (1).

Ethyl 4-ethyl-6-methyl-2-phenylpyridine-3-carboxylate 17

Ethyl 3-amino-3-phenylpropenoate **7a** (0.1 ml, 0.6 mmol) and hex-3-yn-2-one **5c** (0.08 ml, 0.73 mmol) were reacted according to the one-step general procedure (method B, C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale yellow oil (Found: MH^+, 270.1494. $C_{17}H_{19}NO_2$ requires *M*H, 270.1495); ν_{max}(film)/cm^{-1} 2976, 2937, 1723, 1555, 1145, 1086, 1015, 918, 870 and 768; δ_H(400 MHz; $CDCl_3$) 7.48 (2 H, m, *o*-Ph*H*), 7.30 (3 H, m, *m,p*-Ph*H*), 6.96 (1 H, s, Py*H*), 4.00 (2 H, q, *J* 7.6, OC*H*$_2$Me), 2.63 (2 H, q, *J* 7.1, C*H*$_2$Me), 2.52 (3 H, s, Me), 1.18 (3 H, t, *J* 7.6, OCH_2*Me*), 0.88 (3 H, t, *J* 7.1, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 169.5 (C), 159.4 (C), 156.8 (C), 151.9 (C), 140.8 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 126.5 (C), 121.8 (CH), 61.7 (CH_2), 26.6 (CH_2), 25.0 (Me), 15.1 (Me) and 14.0 (Me); *m*/*z* (APcI) 270 (MH^+, 100%), 107 (4), 77 (4) and 59 (49).

Diethyl 2,4-diphenylpyridine-3,6-dicarboxylate 18

Ethyl 3-amino-3-phenylpropenoate **7a** (0.1 g, 0.63 mmol) and ethyl 2-oxo-4-phenylbut-3-ynoate **9b** (0.12 ml, 0.75 mmol) were reacted according to the one-step general procedure (method C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a colourless solid, mp 111–112 °C (light petroleum–ethyl acetate) (Found: C, 73.6; H, 5.7; N, 3.7. $C_{23}H_{21}NO_4$ requires C, 73.6; H, 5.6; N, 3.4%) (Found: MH^+, 376.1549. $C_{23}H_{21}NO_4$ requires *M*H, 376.1550); ν_{max}(Nujol)/cm^{-1} 2925, 1739, 1706, 1246, 1136, 1055, 906, 847, 782, 745 and 700; δ_H(400 MHz; $CDCl_3$) 8.03 (1 H, s, PyH), 7.59 (2 H, m, *o*-PhH), 7.33 (8 H, m, *m,p*-PhH), 4.41 (2 H, q, *J* 7.1, OCH_2), 3.89 (2 H, q, *J* 7.1, OCH_2), 1.34 (3 H, t, *J* 7.1, Me), 0.78 (3 H, t, *J* 7.1, Me); δ_C(100 MHz; $CDCl_3$) 168.3 (C), 165.2 (C), 157.7 (C), 150.1 (C), 148.6 (C), 139.4 (C), 137.8 (C), 131.5 (C), 129.5 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 124.5 (CH), 124.5 (CH), 124.5 (CH), 62.6 (CH_2), 62.1 (CH_2), 14.7 (Me) and 13.8 (Me); *m*/*z* (APcI) 376 (MH^+, 100%), 375 (1) and 270 (2).

Ethyl 2-(2-furyl)-6-methyl-4-(trimethylsilyl)pyridine-3-carboxylate 19

Ethyl 3-amino-3-(2-furyl)propenoate **7b** (0.10 ml, 0.55 mmol) and 4-(trimethylsilyl)but-3-yn-2-one **5a** (0.12 ml, 0.73 mmol) were reacted according to the one-step general procedure (method B or E). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (4 : 1), gave the title compound as a dark oil (Found: MH^+, 304.1369. $C_{16}H_{21}NO_3Si$ requires *M*H, 304.1370); ν_{max}(film)/cm^{-1} 2962, 2898, 1727, 1520, 1165, 1087, 1015, 836 and 757; δ_H(400 MHz; $CDCl_3$) 7.37 (1 H, m, Fu*H*), 7.13 (1 H, s, Py*H*), 6.90 (1 H, m, Fu*H*), 6.43 (1 H, m, Fu*H*), 4.25 (2 H, q, *J* 7.1, CH_2), 2.52 (3 H, s, Me), 1.20 (3 H, t, *J* 7.1, CH_2Me), 0.25 (9 H, s, $SiMe_3$); δ_C(100 MHz; $CDCl_3$) 169.2 (C), 156.9 (C), 147.9 (C), 142.3 (CH), 125.9 (CH), 110.8 (CH), 109.5 (CH), 60.5 (CH_2), 23.6 (Me), 13.0 (Me) and 0.0 (Me); other quaternary carbons not observed; *m*/*z* (APcI) 304 (MH^+, 1%), 141 (2), 117 (100), 107 (26), 90 (8) and 59 (2).

Ethyl 6-methyl-2-(2-pyridyl)-4-ethylpyridine-3-carboxylate 20

Ethyl 3-amino-3-(2-pyridyl)propenoate **7c** (0.1 g, 0.52 mmol) and hex-3-yn-2-one **5c** (0.7 ml, 0.64 mmol) were reacted according to the one-step general procedure (method C or D). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3 : 1), gave the *title compound* as a pale orange oil (Found MH^+, 271.1442. $C_{16}H_{18}N_2O_2$ requires *M*H, 271.1447); ν_{max}(film)cm^{-1} 2975, 2936, 2876, 1729, 1584, 1474, 1384, 1278, 1086, 777, 745 and 687; δ_H(400 MHz; $CDCl_3$) 8.50 (1 H, d, *J* 3.8, 6′-Py*H*), 8.14 (1 H, d, *J* 8.0, 3′-Py*H*), 7.72 (1 H, t, *J* 8.0, 4′-Py*H*), 7.19 (1 H, dd, *J* 3.8, 8.0, 5′-PyH), 7.01 (1 H, s, 5-Py*H*), 4.22 (2 H, q, *J* 7.1, OCH_2), 2.65 (2 H, q, *J* 7.6, CH_2), 2.54 (3 H, s, Me), 1.20 (3 H, t, *J* 7.6, CH_2Me), 1.12 (3 H, t, *J* 7.1, OCH_2Me); δ_C(100 MHz; $CDCl_3$) 169.8 (C), 158.9 (C), 156.9 (C), 153.8 (C), 152.3 (C), 148.5 (CH), 137.2 (CH), 126.4 (C), 123.7 (CH), 123.2 (CH), 123.1 (CH), 61.5 (CH_2), 26.4 (CH_2), 24.9 (Me), 15.1 (Me) and 14.4 (Me); *m*/*z* (APcI) 271 (MH^+, 87%), 226 (13) and 225 (100).

tert-Butyl 2,6-dimethylpyridine-3-carboxylate 21

tert-Butyl β-aminocrotonate **7d** (0.14 g, 0.89 mmol) and 4-(trimethylsilyl)but-3-yn-2-one **5a** (0.19 ml, 1.19 mmol) were reacted according to the one-step general procedure (method E). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (4 : 1), gave the *title compound* as a pale yellow oil (0.15 g, 83%) (Found: MH^+, 208.1337. $C_{12}H_{17}NO_2$ requires *M*H, 208.1337); ν_{max}(film)/cm^{-1} 2977, 2930, 2856, 1720, 1592, 1568, 1127 and 1083; δ_H(400 MHz; $CDCl_3$) 7.95 (1 H, d, *J* 8.0, 4-Py*H*), 6.97 (1 H, d, *J* 8.0, 5-Py*H*), 2.71 (3 H, s, Me), 2.51 (3 H, s, Me), 1.53 (9 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 167.0 (C), 161.4 (C), 159.6 (C), 139.5 (CH), 125.2 (C), 121.2 (CH), 82.4 (C), 29.0 (Me), 25.8 (Me) and 25.5 (Me); *m*/*z* (APcI) 208 (MH^+, 5), 182 (5), 153 (9), 152 (100) and 84 (5).

tert-Butyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate 22

tert-Butyl β-aminocrotonate **7d** (0.1 g, 0.64 mmol) and 3-phenylbut-3-yn-2-one **5b** (0.1 ml, 0.76 mmol) were reacted according to the one-step general procedure (method C, D or E). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (4 : 1), gave the *title compound* as a pale yellow oil (Found: MH^+, 284.1650. $C_{18}H_{21}NO_3$ requires *M*H, 284.1647); ν_{max}(film)/cm^{-1} 2976, 2928, 1722, 1588, 1551, 1138, 1089 and 1031; δ_H(400 MHz; $CDCl_3$) 7.32 (5 H, m, Ph*H*), 6.91 (1 H, s, Py*H*), 2.53 (3 H, s, Me), 2.50 (3 H, s, Me), 1.22 (9 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 168.4 (C), 158.4 (C), 155.0 (C), 148.4 (C), 139.2 (C), 128.7 (CH), 128.7 (CH), 128.6 (CH), 127.5 (C), 121.5 (CH), 82.5 (C), 28.1 (Me), 24.8 (Me) and 23.2 (Me); *m*/*z* (APcI) 284 (MH^+, 100%) and 250 (1).

tert-Butyl 2,6-dimethyl-4-ethylpyridine-3-carboxylate 23

tert-Butyl β-aminocrotonate **7d** (0.1 g, 0.64 mmol) and hex-3-yn-2-one **5c** (0.08 ml, 0.73 mmol) were reacted according to the one-step general procedure (method C, D or E). Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (4 : 1), gave the *title compound* as a pale yellow oil (Found: MH^+, 236.1650. $C_{14}H_{21}NO_2$ requires *M*H, 236.1651); ν_{max}(film)/cm^{-1} 2974, 2932, 1721, 1594, 1562, 1162 and 1092; δ_H(400 MHz; $CDCl_3$) 6.83 (1 H, s, Py*H*), 2.54 (2 H, q, *J* 7.6, C*H*$_2$Me), 2.45 (3 H, s, Me), 2.44 (3 H, s, Me), 1.53 (9 H, s, CMe_3), 1.14, (3 H, t, *J* 7.6, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 171.2 (C), 160.7 (C), 156.5 (C), 152.6 (C), 130.4 (C), 123.1 (CH), 85.0 (C), 30.8 (Me), 28.8 (CH_2), 27.1 (Me), 25.4 (Me) and 17.4 (Me); *m*/*z* (APcI) 236 (MH^+, 100%), 181 (5) and 180 (60).

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