Synthesis of α-Isocyano-α-alkyl(aryl)acetamides and their Use in the Multicomponent Synthesis of 5-Aminooxazole, Pyrrolo[3,4-*b*]pyridin-5-one and 4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridine

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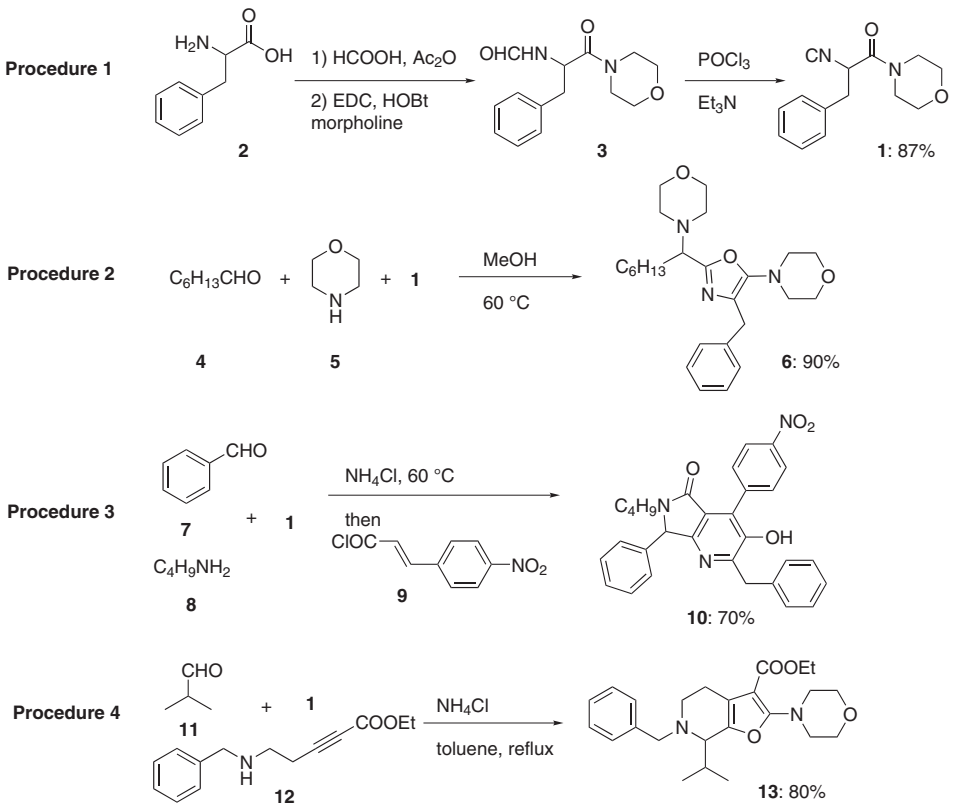
Abstract: α-Isocyano-β-phenylpropionamide **1** is synthesized from the corresponding amino acid in excellent yield. The unique reactivity of this bifunctional compound is exploited for the development of novel multicomponent synthesis of 5-aminooxazole **6**, pyrrolo[3,4-*b*]pyridin-5-one **10** and 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine **13**.

Key words: domino process, multicomponent reaction, heterocycles, isonitrile, oxazole, pyrrolopyridinone, tetrahydrofuropyridine



Scheme 1

Introduction

Multicomponent reaction (MCR) is a process in which three or more reactants are combined in a single reaction flask to produce a product that incorporates substantial portions of all starting materials. By saving synthetic operations while maximizing the buildup of structural and functional complexity, these highly step-economic reactions are particularly appealing in the context of diversity as well as target-oriented syntheses.[1] Isonitrile is one of the key components of the well-known Passerini three-component reaction (P-3CR) and Ugi four-component reaction (U-4CR).[2] A number of isonitriles bearing additional functionalities are known. Among them, α-isocyano acetate[3] and tosylmethyl isocyanide (TosMIC), developed by Schöllkopf[3] and Van Leusen,[4] respectively,

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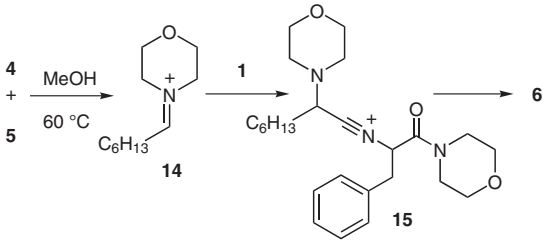
are notable examples and have found wide applications in the synthesis of diverse class of heterocycles. In contrast, the chemistry of α-isocyano acetamide has been relatively underdeveloped.[5] Here we describe a convenient preparation of α-isocyano-β-phenylpropionamide **1** and its use in the development of novel multicomponent reactions for the synthesis of 5-aminooxazole **6**,[6] pyrrolo[3,4-*b*]pyridin-5-one **10**[7] and 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine **13** (Scheme 1).[8]

Scope and Limitations

The (D,L)-α-isocyano-β-phenylpropionamide **1** is synthesized from phenylalanine (**2**) in three conventional steps. *N*-formylation of **2** (HCOOH, Ac_2O) followed by a EDC-mediated amidation with morpholine provided the amide **3** that is dehydrated ($POCl_3$, Et_3N, –20 °C) to afford the desired isocyanide **1** in 87% yield. This transformation is highly reliable and a range of amino acids and dipeptides has been converted to the corresponding isocyano derivatives.[9,10] The dehydration step is racemization-free and the optically pure L-α-isocyano-β-phenylpropionamide **1** has been prepared from L-phenylalanine following the same synthetic sequence. These α-isocyano-α-alkylacetamides are generally odorless and are purified by flash chromatography. They are stable in pure form, but are gradually hydrolyzed back to the *N*-formyl derivatives in a CH_2Cl_2 solution.

The presence of both isocyano and carbonyl (or tosyl) groups rendered the α-methylene proton of TosMIC, α-isocyano acetate and α-isocyano acetamide acidic. Therefore, both the divalent isonitrile carbon and the α-methylene carbon are potentially nucleophilic. It follows that different reaction sequences can be envisaged if the relative reactivity of these two nucleophilic sites can be modulated. Indeed, the rich chemistry of α-isocyano acetate and TOSMIC is mainly based on the nucleophilicity of the α-methylene carbon and several multicomponent reactions have been developed based on this reactivity.[11,12] In contrast, α-isocyano-β-phenylpropionamide **1** displayed different reactivity profile presumably due to the reduced acidity of the α-CH. As shown in Scheme 2, when a solution of an equimolar amount of heptanal, morpholine and **1** was heated to 60 °C for 4 hours, the 5-aminooxazole **6** was obtained in 90% isolated yield. In this transformation, the in situ generated iminium species was attacked by the isonitrile, rather than the α-carbon leading to the nitrilium intermediate **15** that was trapped intramolecularly by the amide oxygen to afford ultimately the 5-aminooxazole **6**.[6]



Scheme 2

This three-component reaction took place smoothly in MeOH without any activator. It was subsequently discovered that the same transformation took place in non-polar aprotic solvent like toluene, in the presence of a suitable additive. The following Lewis acids: $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, Cu(OTf), $Zn(OTf)_2$, CuBr, LiBr, $SiCl_4$ and Brönsted acids: NH_4Cl, $Et_3N{\cdot}HCl$, Bu_4NCl, pyridine·HCl, lutidine·HCl, camphorsulfonic acid have been examined. The cheapest and the readily available NH_4Cl turned out to be the promoter of choice. Although a stoichiometric amount of NH_4Cl was generally used, the reaction might be catalytic in nature since NH_4Cl was scarcely soluble in toluene. It is worth noting that the same reaction occurred sluggishly in toluene in the absence of NH_4Cl.

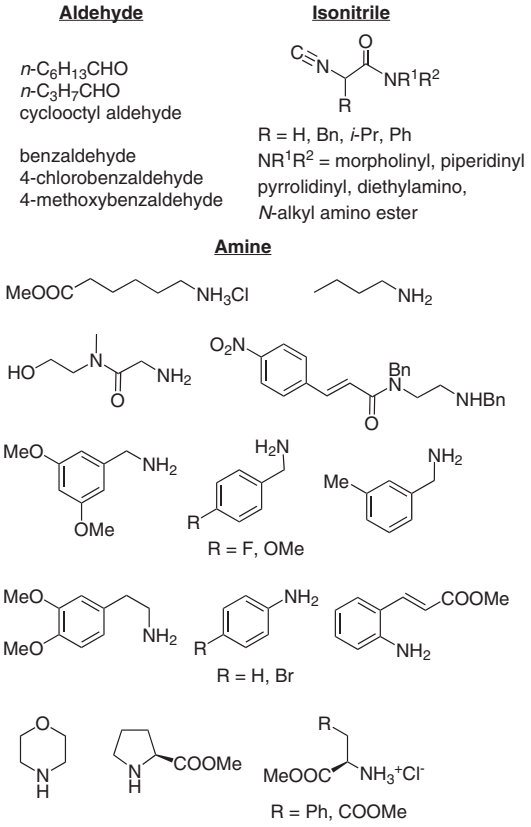
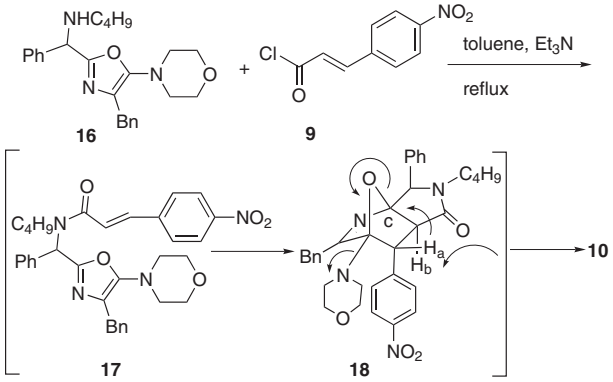


Figure 1

The scope of this reaction has been examined. As shown in the Figure 1, a large set of aldehydes, amines and isonitriles having different functionalities are tolerated. When a hydrochloride salt of an amine was used as an input, in situ neutralization with Et_3N in toluene followed by addition of aldehyde and isonitrile produced the corresponding 5-aminooxazole. Apparently, the stoichiometric amount of $Et_3N{\cdot}HCl$, generated in situ, promoted efficiently the subsequent multicomponent assembly process.

The 5-aminooxazole possesses several potentially reactive functions. Consequently, a domino process could be

expected if it were combined with another polyfunctionalized substrate. One such example is illustrated in the Scheme 3. Thus, simply heating a solution of oxazole **6** and acyl chloride **9** in toluene in the presence of five equivalent of Et_3N led to the formation of medicinally relevant pyrrolo[3,4-*b*]pyridin-5-one (**10**) in excellent yield (Scheme 3). From results of control experiments, a sequence of reaction involving intermolecular acylation-intramolecular Diels–Alder (D–A) cycloaddition-retro-Michael cycloreversion was proposed to explain the formation of compound **10**.

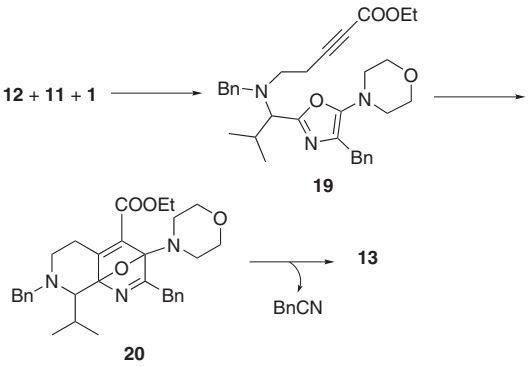


Scheme 3

By combining this bimolecular domino process with the three-component synthesis of 5-aminooxazole, a one-pot four-component assembly of pyrrolopyridinone is subsequently developed.[7] Thus a solution of benzaldehyde (**7**), *n*-butylamine (**8**) and an isonitrile (**1**) in the presence of 1.5 equivalents of NH_4Cl was stirred at 60 °C. Once the oxazole formation deemed complete by TLC analysis, *p*-nitro cinnamoyl chloride (**9**) and Et_3N were added at 0 °C. Heating to reflux produced pyrrolopyridinone **10** in good to excellent yield (Scheme 1, procedure 3). It is interesting to note that six different functionalities participate in this one-pot process, leading to the formation of a bicyclic ring system with the creation of five chemical bonds. The efficiency of this MCR is thus truly remarkable if one looks at the yield per chemical bond formation.

Using funtionalized amine input such as 5-aminopentynoate **12**, a three-component synthesis of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine **13** has been developed.[8] Thus refluxing a toluene solution of *iso*-butyraldehyde (**11**), amine **12** and isocyanide **1** furnished **13** in 80% yield. The outcome of this reaction can be explained by the following reaction sequence. The oxazole **19**, assembled by a three-component process, underwent intramolecular D–A cycloaddition leading to the oxa-bridged tricycle **20**. Fragmentation of **20** by a retro D–A reaction provided then the bicycle **13**. Five chemical bonds are formed in this experimentally simple multicomponent reaction, thus creating a significant molecular complexity (Scheme 4).

In summary, readily accessible α-isocyano-α-alkyl-acetamide **1** displayed different reactivity profile relative to α-



Scheme 4

isocyanoacetate and TosMIC. By judicious selection of reaction partners, several multicomponent reactions have been developed for the synthesis of a range of heterocycles.[13]

Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were recorded on a Nicolet-205 FT-IR spectrometer. ^1H NMR spectra were measured on Bruker AC-250 (250 MHz), AC-300 (300 MHz) and AC-400 (400 MHz) spectrometers with tetramethylsilane as internal standard (δ ppm). Solvents were of ACS grade and were distilled prior to use. Reagents were purified according to standard laboratory techniques. All reactions requiring anhydrous conditions or an inert atmosphere were conducted under an atmosphere of argon.

Procedures

We described in this article four procedures. **Procedure 1** concerns the synthesis of α-isocyano-β-phenylpropionamide **1**, while **Procedures 2–4** deal with the multicomponent synthesis of heterocycles based on the unique reactivity of isocyanide **1**. Specifically, three-component synthesis of 5-aminooxazole **6** is described in **Procedure 2**, a four component assembly of pyrrolo[3,4-*b*]pyridin-5-one **10** in **procedure 3** and a three-component synthesis of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine **13** in **Procedure 4**.

Procedure 1: *N*-(1-Benzyl-2-morpholin-4-yl-2-oxo-ethyl) Formamide (3); Typical Procedure

Acetic anhydride (17.0 mL, 180.2 mmol, 7.2 equiv) was added dropwise to a solution of phenylalanine (4.13 g, 25.0 mmol, 1.0 equiv) in HCOOH (50.0 mL) at 5 °C. After the addition was complete, the reaction mixture was stirred at r.t. for an additional 1 h. Ice-water (20.0 mL) was added and the mixture was concentrated at reduced pressure to give the analytically pure white crystalline *N*-formylphenylalanine (quant. yield; mp 163–165 °C).

To a solution of *N*-formylphenylalanine (3.66 g, 19.0 mmol, 1.0 equiv) and morpholine (2.0 mL, 22.9 mmol, 1.2 equiv) in anhyd CH_2Cl_2 (50.0 mL) were added Et_3N (3.2 mL, 23.2 mmol, 1.2 equiv), HOBt (3.11 g, 23.0 mmol, 1.2 equiv) and EDC (4.41 g, 23.0 mmol, 1.2 equiv) successively and the reaction mixture was stirred for 24 h at r.t. The reaction mixture was diluted with sat. NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhyd Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: heptane–EtOAc, 1:1 then EtOAc or CH_2Cl_2–MeOH, 30:1) to give the amide **3** (yield 97%; colorless oil).

***N*-Formylphenylalanine**

^1H NMR (250 MHz, MeOD): δ = 8.03 (s, 1 H), 7.25 (m, 5 H), 4.77 (dd, *J* = 8.2, 5.2 Hz, 1 H), 3.24 (dd, *J* = 14.0, 5.2 Hz, 1 H), 3.01 (dd, *J* = 14.0, 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, MeOD): δ = 174.1, 163.5, 138.0, 130.3 (2 C), 129.5 (2 C), 127.9, 53.6, 38.4.

***N*-(1-Benzyl-2-morpholin-4-yl-2-oxo-ethyl) Formamide (3)**

IR ($CDCl_3$): 3414, 3004, 2864, 1683, 1637, 1445, 1116 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.19–7.31 (m, 5 H), 6.68 (br s, 1 H), 5.23 (m, 1 H), 3.60–3.24 (m, 6 H), 3.08 (dd, *J* = 13.0, 5.3 Hz, 1 H), 2.98 (dd, *J* = 13.0, 9.3 Hz, 1 H), 2.94–2.88 (m, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.6, 160.5, 135.8, 129.5, 128.6, 127.3, 66.3, 66.0, 48.1, 46.0, 42.3, 39.8.

MS (EI): *m*/*z* = 262 [M]$^+$.

2-Isocyano-1-morpholin-4-yl-3-phenyl-propan-1-one (1)

A stirred solution of morpholinyl amide of *N*-formyl phenylalanine (4.85 g, 18.5 mmol, 1.0 equiv) and Et_3N (12.8 mL, 92.0 mmol, 5.0 equiv) in anhyd CH_2Cl_2 (90.0 mL) was cooled to –20 °C to –30 °C. Phosphorus oxychloride (2.6 mL, 27.5 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred for 3 h at –20 °C to –30 °C. An aq sat solution of Na_2CO_3 was introduced dropwise so that the temperature of mixture was maintained at –20 °C to –30 °C. The mixture was stirred for 0.5 h and raised to r.t. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: heptane–EtOAc, 2:1) to provide the isocyanide **1** (yield: 87%; white solid; mp 74–78 °C).

IR ($CDCl_3$): 2928, 2863, 2142, 1668, 1496, 1456, 1116 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 5 H), 4.54 (dd, *J* = 7.7, 7.0 Hz, 1 H), 3.20–3.69 (m, 10 H).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 163.5, 159.8, 135.0, 129.4 (2 C), 128.8 (2 C), 127.7, 66.4, 65.9, 55.0, 46.2, 42.9, 39.1.

MS (EI): *m*/*z* = 244 [M]$^+$.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.71; H, 6.54; N, 11.47.

Procedure 2: Three-Component Synthesis of 5-Aminooxazole (6) in MeOH; Typical Procedure

A solution of morpholine (17.0 μL, 19.5 μmol, 1.3 equiv) and heptanal (24.0 μL, 17.9 μmol, 1.2 equiv) in anhyd MeOH (1.0 mL) was stirred at r.t. for 30 min. Isocyanoacetamide **1** (36.0 mg, 14.7 μmol, 1.0 equiv) was then added. The reaction mixture was stirred at 60 °C and the reaction course was followed by TLC. After the disappearance of isonitrile **1** (typically 4 h), the reaction mixture was cooled to r.t. and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, eluent: EtOAc–heptane, 2:1) to give the corresponding oxazole (yield 90%, colorless oil).

Ammonium chloride-promoted three-component synthesis of 5-amino oxazole (6) in toluene

A solution of morpholine (57.0 μL, 65.4 μmol, 1.3 equiv) and heptanal (81 μL, 60.3 μmol, 1.2 equiv) in anhyd toluene (3.3 mL) was stirred at r.t. for 30 min. Isocyanoacetamide **1** (122 mg, 50.0 μmol, 1 equiv) and NH_4Cl (40 mg, 74.8 μmol, 1.5 equiv) were added, successively. The reaction mixture was stirred at 60 °C and followed by TLC (typically 4 h). After the disappearance of isonitrile, the reaction mixture was cooled to r.t., diluted with aq Na_2CO_3 and was extracted with EtOAc. The combined organic phase was washed by brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, eluent: EtOAc–heptane, 2:1) to give the corresponding oxazole (**6**) (yield 81%, colorless oil).

IR ($CHCl_3$): 3622, 2967, 2401, 1663, 1495, 1453, 1376, 1231, 1114 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.24 (m, 5 H), 3.83 (s, 2 H), 3.70 (m, 8 H), 3.57 (dd, *J* = 8.4, 6.8 Hz, 1 H), 2.96 (m, 4 H), 2.57 (ddd, *J* = 11.6, 5.6, 3.7 Hz, 2 H), 2.48 (ddd, *J* = 11.6, 5.6, 3.7 Hz, 2 H), 1.86 (m, 2 H), 1.25 (m, 8 H), 0.86 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 151.9, 139.6, 128.3 (3 C), 126.1 (2 C), 124.1, 67.3, 66.8 (3 C), 63.2, 51.0 (3 C), 50.1, 31.8, 31.6, 29.8, 28.9, 26.2, 22.5, 14.0.

MS (ESI): *m*/*z* = 450.2 [M]$^+$.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{37}N_3O_3$: 450.2733; found: 450.2733.

Anal. Calcd for $C_{25}H_{37}N_3O_3$: C, 70.22; H, 8.72; N, 9.83. Found: C, 69.89; H, 8.76; N, 9.78.

Procedure 3: Four-Component Synthesis of Pyrrolo[3,4-*b*]pyridin-5-one (10); Typical Procedure

To a solution of *n*-butylamine (19.0 μL, 19.7 μmol, 1.3 equiv) in anhyd toluene (1.0 mL), was added benzaldehyde (18.0 μL, 17.7 μmol, 1.2 equiv). After being stirred at r.t. for 30 min, isocyanide (36.0 mg, 14.7 μmol, 1.0 equiv), NH_4Cl (12.0 mg, 22.4 μmol, 1.5 equiv) were added, successively. The reaction mixture was stirred at 60 °C until the disappearance of isonitrile **1**. The reaction mixture was cooled to 0 °C and diluted with toluene (1.0 mL). Et_3N (104.0 μL, 74.8 μmol, 5.0 equiv) was added followed by acid chloride **9** (80.0 mg, 37.8 μmol, 2.5 equiv) in small portion. Stirring was continued at r.t. for 30 min and at reflux for 12 h. After cooling the mixture to r.t., the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, eluent: CH_2Cl_2–acetone, 99:1) to give the corresponding pyrrolopyridine **10** (yield 70%; yellow oil).

IR ($CDCl_3$): 3550, 3009, 2962, 2932, 2874, 1682, 1603, 1523, 1494, 1455, 1381, 1349, 1314, 1237, 1120, 1064, 854 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 8.3 Hz, 2 H), 7.43–7.21 (m, 10 H), 5.46 (s, 1 H), 5.18 (br s, 1 H), 4.23 (d, *J* = 14.1 Hz, 1 H), 4.19 (d, *J* = 14.1 Hz, 1 H), 3.84 (ddd, *J* = 14.0, 7.7, 7.7 Hz, 1 H), 3.29 (ddd, *J* = 14.0, 8.1, 6.0 Hz, 1 H), 1.48 (m, 2 H), 1.26 (sext, *J* = 7.3 Hz, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 157.8, 153.3, 148.1, 146.9, 137.5, 136.5, 135.6, 131.3, 130.3, 129.1, 129.0, 128.9, 128.7, 127.8, 126.8, 123.6, 120.6, 64.5, 40.1, 30.2, 20.1, 13.6.

MS (CI): *m*/*z* = 494 [M + H]$^+$.

Procedure 4: Ammonium Chloride-Promoted Three Component Synthesis of 4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridine (13); Typical Procedure

A solution of amine **12** (100.0 mg, 43.3 μmol, 1.2 equiv) and *iso*-butyraldehyde (39.0 μL, 42.8 μmol, 1.2 equiv) in anhyd toluene (3.6 mL) was stirred at r.t. in the presence of NH_4Cl (19.2 mg, 36.0 μmol, 1.0 equiv) for 1 h. α-Isocyanoacetamide **1** (88.0 mg, 36.0 μmol, 1.0 equiv) was added and the reaction mixture was heated to reflux. The reaction was monitored by TLC (15 h). The reaction mixture was cooled to r.t. and toluene was removed under reduced pressure. After dilution with water, the product was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, eluent: heptane–EtOAc, 3:1) to give the corresponding furopyridine **13** (yield 80%; yellow oil).

IR ($CHCl_3$): 2960, 2867, 1686, 1573, 1494, 1448, 1367, 1296, 1271, 1171, 1115, 1087 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.31 (m, 5 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.75 (t, *J* = 4.7 Hz, 4 H), 3.57 (s, 2 H), 3.32–3.47 (m,

4 H), 2.92 (m, 1 H), 2.87 (d, *J* = 8.2 Hz, 1 H), 2.63–2.73 (m, 2 H), 2.40 (m, 1 H), 1.81 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 161.3, 143.2, 139.9, 128.9 (2 C), 128.2 (2 C), 127.0, 116.6, 94.4, 66.8 (2 C), 63.1, 59.8, 57.9, 48.9 (2 C), 44.3, 32.7, 20.9, 20.7, 19.5, 14.6.

MS (ESI): *m*/*z* = 413.2 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{32}N_2O_4$: 435.2260; found: 435.2259.

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.77; H, 8.04; N, 6.61.

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