Four-Component Synthesis of Functionalized 2,2′-Bipyridines Based on the Blaise Reaction

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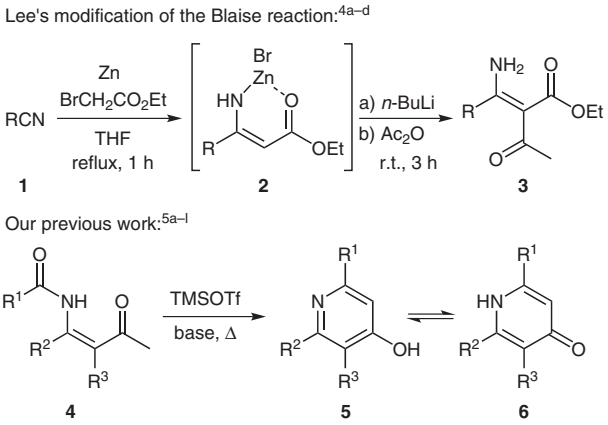
Abstract: In situ C-acylation of the Blaise intermediate – as reported by Lee and coworkers – provides α-acyl-β-enamino esters that are versatile building blocks for the preparation of N-heterocycles. The corresponding N-acylated β-ketoenamides can be employed in the synthesis of 4-hydroxypyridine derivatives. N-Acylation of the α-acyl-β-enamino esters with 2-picolyl chloride furnished β-ketoenamides, and the subsequent TMSOTf/base-promoted intramolecular condensation reaction led to 4-hydroxy-2,2′-bipyridine derivatives. Conversion into 2,2′-bipyrid-4-yl nonaflates allowed further functionalization such as palladium-catalyzed coupling reactions.

Key words: condensation, 2,2′-bipyridines, β-ketoenamides, multicomponent reaction, nonaflates, pyridines

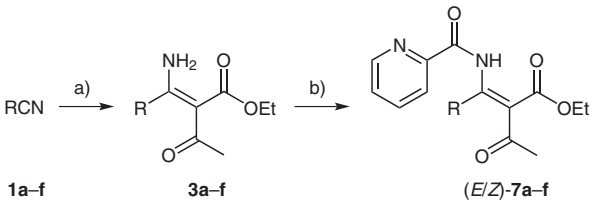
Although being first described at the beginning of the 20th century, the synthetic potential of the Blaise reaction[1] – the addition of zinc enolates derived from α-halo esters to nitriles – has not been fully exploited. Despite the broad availability of suitable starting materials application of this reaction was limited due to low yields and competing side reactions. More recently, improved protocols led to an increased interest.[2] Developments and applications of the Blaise reaction have been reviewed by Rao et al.[3] Lee and coworkers demonstrated that zinc chelate intermediates such as **2** (Scheme 1) react in situ with electrophiles to provide valuable precursors for the synthesis of heterocycles like pyrroles,[4a,b] 2-pyridones,[4c] or indoles.[4d] Following our previous work[5] on the trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted intramolecular condensation of β-ketoenamides **4** to 4-hydroxypyridines **5**[6] we were interested in expanding the substrate scope for this transformation. In particular we were intrigued to extend our method to the synthesis of unsymmetrically functionalized 2,2′-bipyridines[5f] taking into account the general importance[7] of this class of heterocycles in coordination and supramolecular chemistry and in numerous applications. Various cross-coupling strategies employing pyridine-containing building blocks and other de novo approaches for their synthesis have been developed.[8,9] However, new and flexible approaches for the synthesis of unsymmetrically functionalized 2,2′-bipyridines are rare.

Upon treatment with *n*-butyllithium followed by addition of acetic acid anhydride the intermediates **2** of the Blaise reaction of ethyl bromoacetate with nitriles **1** are transformed into α-acyl-β-enamino esters **3** (Scheme 1).[4a] Being structurally related to β-ketoenamides **4**, we envisioned that N-acylation of the α-acyl-β-enamino esters **3** (with activated carboxylic acid derivatives) should also provide suitable precursors for the TMSOTf-promoted cyclization to 4-hydroxypyridine derivatives.



Scheme 1 C-Acylation of the Blaise intermediates **2** leading to **3** and TMSOTf/base-promoted intramolecular condensation of β-ketoenamides **4** to 4-hydroxypyridines **5**

Following Lee's protocol[4a] we prepared a series of α-acyl-β-enamino esters **3** that were acylated[10] with activated picolinic acid derivatives (Scheme 2). The desired β-ketoenamides **7a–f** were obtained as inseparable mixtures of *E* and *Z* isomers[11] in moderate to good yields (Table 1).



Scheme 2 Synthesis of α-acyl-β-enamino esters **3a–f** and N-acylation to β-ketoenamides **7a–f**. *Reagents and conditions*: (a) i) Zn (activated, 2 equiv), $BrCH_2CO_2Et$ (1.5 equiv), THF, reflux, 1 h; ii) *n*-BuLi (1 equiv), 0 °C; iii) Ac_2O (1.3 equiv), r.t., 3 h.[4a] (b) Method A: 2-PyCOCl (2 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C then r.t., overnight; method B: 2-PyCOBt[12] (1.5 equiv), NaH (1.3 equiv), THF, r.t., overnight.

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Table 1 Synthesis and N-Acylation of α-Acyl-β-enamino Esters **3a–f** to Intermediates **7a–f**

R	Yield of **3** (%)[a,b]	Method for N-acylation	Yield of **7** (%)[a]	Isomeric ratio[c]
Ph	**3a**: 63	A	**7a**: 87	3.5:1
CH_2OMe	**3b**: 23[d]	A	**7b**: 42	–[e]
Me	**3c**: 51[f]	A	**7c**: 50	3.0:1
i-Pr	**3d**: 54[f]	A	**7d**: 61	4.5:1
n-Bu	**3e**: 71	B	**7e**: 71	4.0:1
4-NCC_6H_4	**3f**: 36[g]	A	**7f**: 83	16:1

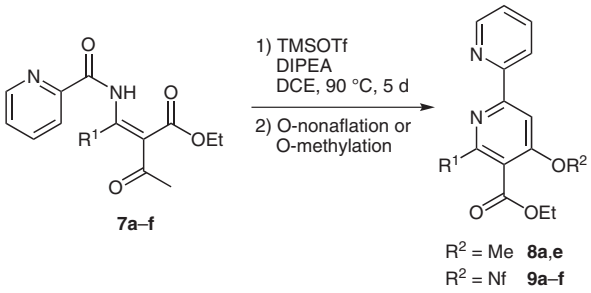
[a] Yield of pure compounds after column chromatography.
[b] For preparation of **3a**, **3c**, and **3d**, also see ref. 4a.
[c] Ratio determined by ^{1}H NMR spectroscopy.
[d] For an alternative preparation of **3b**, also see ref.[13].
[e] Compound **7b** could not be obtained in pure form and the isomeric ratio could not be determined by ^{1}H NMR spectroscopy.
[f] Nitriles **1c** and **1d** were used as solvent in the Blaise reaction (yields of **3c** and **3d** refer to $BrCH_2CO_2Et$).
[g] Twice the amounts of reagents were used in the modified Blaise reaction [compound **3g** was isolated in 21% yield as byproduct (also see Scheme 4)].

Gratifyingly, the mixtures of *E*- and *Z*-configured β-ketoenamides **7** (except **7b**) cyclized in the desired manner: treatment with TMSOTf in the presence of Hünig base (DIPEA) and heating for 5 days in 1,2-dichloroethane (DCE) provided the desired 4-hydroxy-2,2′-bipyridines (Table 2). However, their isolation directly after the cyclization posed to be rather difficult: separation from the ammonium salt generated from Hünig base and trifluoromethanesulfonic acid (formed after aqueous workup) was tedious, requiring several runs of column chromatography. This problem was solved when the crude 4-hydroxy-2,2′-bipyridines were directly O-alkylated to **8**, or more conveniently O-nonaflated to **9**.[14,15]

The decreased polarity of 2,2′-bipyrid-4-yl nonaflates **9** allows their facile chromatographic purification. An additional advantage of this protocol is the direct preparation of precursors for subsequent metal-catalyzed coupling reactions. Although the overall yields for the synthesis of 2,2′-bipyridine derivatives **8** or **9** are sometimes only moderate, the readiness and simplicity of the protocol is remarkable. No systematic optimizations have so far been attempted.

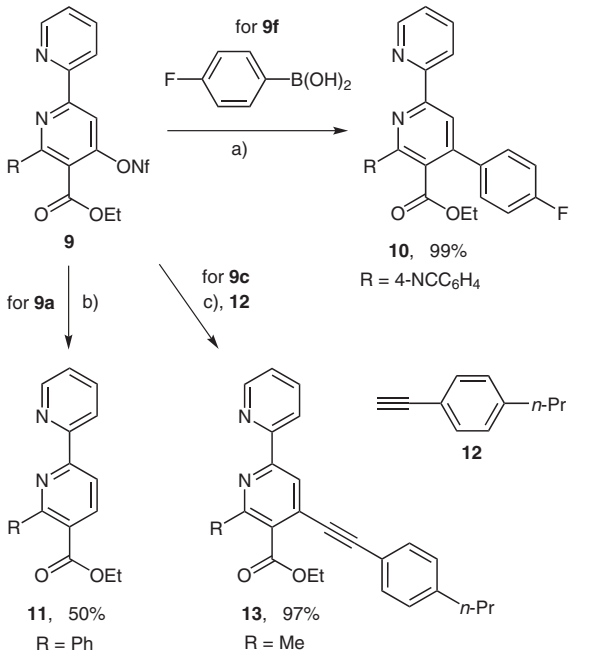
We performed a few typical subsequent palladium-catalyzed transformations employing the obtained 2,2′-bipyrid-4-yl nonaflates **9** in order to demonstrate their synthetic potential (Scheme 3). Reduction of nonaflate **9a** by formic acid and triethylamine[17] provided 2,2′-bipyridine derivative **11** in moderate yield. Suzuki coupling of nonaflate **9f** with 4-fluorophenyl boronic acid furnished 2,2′-bipyridine **10** and Sonogashira reaction of **9c** with alkyne **12** led to 2,2′-bipyridine **13**, both in excellent yields.

Table 2 TMSOTf/Base-Promoted Cyclization of β-Ketoenamides **7** to Unsymmetrically Substituted 2,2′-Bipyridine Derivatives **8** or **9**



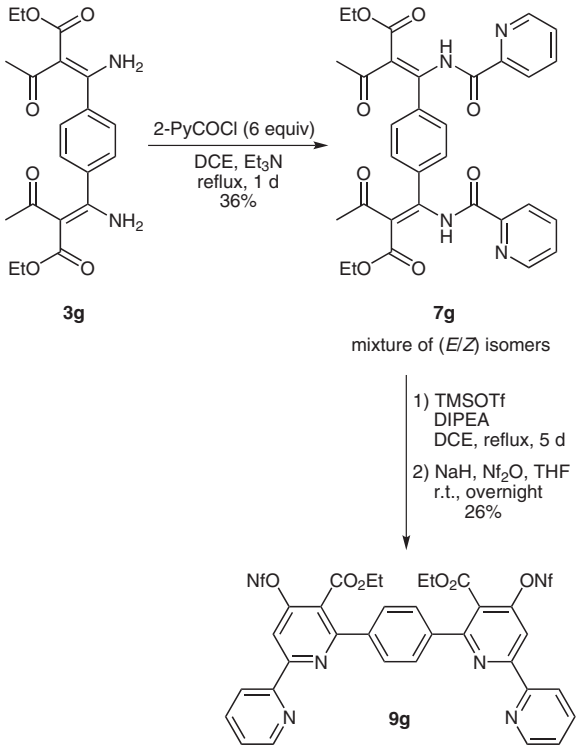
Entry	R^1	Derivatization	Yield (%)[a]
1	**7a**: Ph	methylation[b]	**8a**: 67
2	**7a**: Ph	nonaflation[c]	**9a**: 70
3	**7b**: CH_2OMe	nonaflation[c]	**9b**: –[d]
4	**7c**: Me	nonaflation[c]	**9c**: 67
5	**7d**: *i*-Pr	nonaflation[c]	**9d**: 33
6	**7e**: *n*-Bu	methylation[b]	**8e**: 70
7	**7e**: *n*-Bu	nonaflation[c]	**9e**: 61
8	**7f**: 4-NCC_6H_4	nonaflation[c]	**9f**: 62

[a] Yields of pure products after column chromatography.
[b] MeI, K_2CO_3, acetone, reflux, overnight.
[c] NaH, Nf_2O, THF, r.t., overnight.[16]
[d] Decomposition of starting material.



Scheme 3 Subsequent transformations of the 2,2′-bipyrid-4-yl nonaflates **9**. *Reagents and conditions*: (a) K_2CO_3, $Pd(PPh_3)_4$ (5 mol%), DMF, 80 °C, 3 h; (b) HCO_2H, Et_3N, dppp (20 mol%), $Pd(OAc)_2$ (10 mol%), DMF, 80 °C, 2 h; (c) CuI (5 mol%), $Pd(PPh_3)_2Cl_2$ (5 mol%), DMF–Et_3N (1:1), 60 °C, overnight.

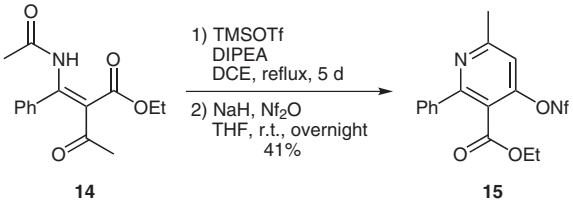
In addition to monoaddition product **3f** the modified Blaise reaction of terephthalodinitrile **1f** also afforded the bis-β-enamino ester **3g** with 21% yield (Scheme 4). N-Acylation leading to **7g** was challenging due to the poor solubility of precursor **3g** in all solvents examined. The subsequent TMSOTf/base-promoted cyclization followed by nonaflation allowed the synthesis of bis-2,2′-bipyridyl nonaflate **9g** in low overall yield (Scheme 4). Although further optimization should be possible this first example nevertheless demonstrates that the presented approach allows a simple and very rapid access to fairly complex compounds with 2,2′-bipyridyl moieties.



Scheme 4 Synthesis of phenylene bridged bis(2,2′-bipyrid-4-yl) derivative **9g**

The modified Blaise reaction of benzonitrile **1a** was also performed with longer reaction times. In addition to the expected product **3a** we also obtained β-ketoenamide **14** in 8% yield formed by partial N-acylation of **3a** with the excess of Ac_2O. Treatment of compound **14** with TMSOTf and base followed by nonaflation afforded the pyrid-4-yl nonaflate **15** in moderate yield (Scheme 5), indicating that the presented approach is not limited to the synthesis of 2,2′-bipyridine derivatives, but may also be utilized for the synthesis of highly functionalized pyridine derivatives in general if other N-acylating components are used.

We demonstrated that Lee's modification of the Blaise reaction followed by N-acylation provides highly suitable precursors for the TMSOTf/base-promoted intramolecular condensation affording 4-hydroxypyridine derivatives in moderate to good yields. Moreover, a flexible method



Scheme 5 Synthesis of pyrid-4-yl nonaflate **15**

for the preparation of unsymmetrically functionalized 2,2′-bipyridine derivatives has been discovered. The introduction of the nonaflyl group in 4-position allows metal-catalyzed coupling reactions providing ideal building blocks for more complex architectures.

Acknowledgment

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(10) **Representative Procedure for the N-Acylation of α-Acyl-β-enamino Esters with 2-Picolyl Chloride: Ethyl 3-oxo-2-[phenyl(picolinamido)methylene]butanoate (7a)**
$SOCl_2$ (0.29 mL, 4.00 mmol) was added dropwise to a solution of 2-picolinic acid (492 mg, 4.00 mmol), and Et_3N (0.55 mL, 4.00 mmol) in CH_2Cl_2 (13 mL) under an argon atmosphere. After addition of catalytic amounts of DMF the mixture was stirred for 4 h at r.t. A solution of α-acyl-β-enamino ester **3a** (467 mg, 2.00 mmol) in CH_2Cl_2 (7 mL) was added at 0 °C. While stirring overnight the mixture was allowed to warm up to r.t. (in some cases conversion of the starting material was complete after a few hours) and sat. aq $NaHCO_3$ solution (20 mL) was added. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were dried with Na_2SO_4, and after filtration the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (silica gel, hexane–EtOAc = 4:1 → 2:1) afforded 590 mg (87%) of **7a** (major/minor isomer ca. 3.5:1) as brownish oil. IR (ATR): 3170 (NH), 3060 (=CH), 2980, 2930 (CH), 1710 (C=O), 1650, 1550 (C=C, C=N) cm^{-1}. Chemical shifts are listed for the major isomer only. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.39 (s, 3 H, $COCH_3$), 3.84 (q, *J* = 7.1 Hz, 2 H, OCH_2), 7.33–7.44 (m, 5 H, Ph), 7.48 (ddd, *J* = 7.7, 4.5, 1.0 Hz, 1 H, 5′-H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1 H, 4′-H), 8.04 (d_{br}, *J* = 7.7 Hz, 1 H, 3′-H), 8.78 (d_{br}, *J* = 4.5 Hz, 1 H, 6′-H) ppm; the NH signal could not be detected. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.4 (q, CH_3), 29.7 (q, $CO\mathit{C}H_3$), 61.2 (t, OCH_2), 116.7 (s, $\mathit{C}COCH_3$), 123.2 (d, C-3′), 127.0 (d, C-5′), 127.5, 127.9, 129.3, 134.5 (3 d, s, Ph), 137.4 (d, C-4′), 148.8 (d, C-6′), 149.2 (s, C-2′), 153.4 (s, CNH), 163.3 (s, CONH), 168.0 (s, $\mathit{C}O_2Et$), 197.3 (s, $\mathit{C}OCH_3$) ppm. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{18}N_2O_4Na$ $[M + Na]^+$: 361.1164; found: 361.1166. Anal. calcd for $C_{19}H_{18}N_2O_4$ (338.4): C, 67.44; H, 5.36; N, 8.28; found: C, 66.80; H, 5.28; N, 8.16.

(11) Whether already the α-acyl-β-enamino esters **3** were isolated as mixtures of *E* and *Z* isomers (no isomerization could be detected by NMR spectroscopy), or isomerization occurred during N-acylation or chromatography of the β-keto-enamides **7** is currently unclear.

(12) 2-PyCOBt = 1*H*-1,2,3-benzotriazol-1-yl(pyrid-2-yl)-methanone; for its preparation, see: (a) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. For a review on *N*-acylbenzotriazoles, see: (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656.

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(15) **Representative Procedure for the Cyclization of β-Ketoenamides Followed by Nonaflation of the Crude Product – 5-Ethoxycarbonyl-6-phenyl-2,2′-bipyrid-4-yl Nonaflate (9a)**
TMSOTf (0.94 mL, 5.17 mmol) was added dropwise to a solution of β-ketoenamide **7a** (350 mg, 1.03 mmol) and DIPEA (0.68 mL, 4.14 mmol) in DCE (25 mL) under argon. The mixture was stirred for 5 d at 90 °C in a sealed tube. All volatile components were removed under reduced pressure, the crude product was dissolved in THF (15 mL) and treated with an excess of NaH (309 mg, 7.73 mmol, 60% in mineral oil, washed with hexane prior to use). After addition of Nf_2O (778 mg, 1.34 mmol) the mixture was stirred overnight at r.t. and then quenched by slow addition of sat. aq NH_4Cl solution (20 mL). The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were dried with Na_2SO_4, and after filtration the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (silica gel, hexane–EtOAc = 40:1 → 20:1) afforded 434 mg (70%) of **9a** as colorless oil. IR (ATR): 3070 (=CH), 2985, 2940–2930, 2905 (CH), 1735 (C=O), 1600, 1575, 1545 (C=C, C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3 H, CH_3), 4.26 (q, *J* = 7.1 Hz, 2 H, OCH_2), 7.40 (ddd, *J* = 7.8, 4.7, 0.8 Hz, 1 H, 5′-H), 7.47–7.50, 7.71–7.74 (2 m, 3 H, 2 H, Ph), 7.85 (td, *J* = 7.8, 1.3 Hz, 1 H, 4′-H), 8.49 (s, 1 H, 3-H), 8.54 (d_{br}, *J* = 7.8 Hz, 1 H, 3′-H), 8.74 (ddd, *J* = 4.7, 1.3, 0.8 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.5 (q, CH_3), 62.6 (t, OCH_2), 111.2 (d, C-3), 121.7 (d, C-5), 121.9 (s, C-3′), 125.1 (d, C-5′), 128.5, 128.6, 129.6 (3 d, Ph), 137.2 (d, C-4′), 138.5 (s, Ph), 149.4 (d, C-6′), 153.5, 155.0, 159.1, 159.4 (4 s, C-2, C-2′, C-4, C-6), 164.2 (s, CO_2Et) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –125.6 (td, *J* = 13.7, 4.4 Hz, 2 F, CF_2), –120.5 (m_c, 2 F, CF_2), –108.7 (t, *J* = 13.7 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.7 Hz, 3 F, CF_3) ppm. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{16}F_9N_2O_5S$ $[M + H]^+$: 603.0636; found: 603.0629. Anal. calcd for $C_{23}H_{15}F_9N_2O_5S$ (602.4): C, 45.86; H, 2.51; N, 4.65; S, 5.32. Found: C, 45.75; H, 2.51; N, 4.69; S, 5.47.

(16) Nf_2O = nonafluorobutanesulfonic acid anhydride; nonaflation employing nonafluorobutanesulfonyl fluoride (NfF) was slow and incomplete.

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