JOC Note

A Cascade Approach to Pyridines from 2-Azido-2,4-dienoates and α-Diazocarbonyl Compounds

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A one-pot synthesis of substituted pyridines via a cascade reaction of 2-azido-2,4-dienoates with α-diazocarbonyl compounds and triphenylphosphine is reported. The process involves a Staudinger−Meyer reaction, a Wolff rearrangement, an aza-Wittig reaction, and an electrocyclic ring-closure. The procedure is general and efficient. The substrates are readily available.

Substituted pyridines are an important class of compounds due to their abundance in biologically important natural and synthetic substances and their utilities as intermediates in synthetic chemistry.[1] Not surprisingly, a large amount of work has been devoted to the development of methods to provide these products in a straightforward fashion,[2] the majority of which involve the transition metal mediated cycloadditions,[3] one-pot multicomponent reactions,[4] and 6π-electrocyclization of the in situ generated azahexa-1,3,5-trienes.[5] Ketenimines are nitrogenated heterocumulenes, which can participate in a variety of organic reactions,[6] such as nucleophilic-addition reactions,[7] radical-addition reactions,[8] [2+2] and [2+4] cycloaddition reactions,[9] and sigmatropic rearrangements.[10] Herein, we describe a cascade synthesis of substituted pyridines via the ketenimine intermediates.

In the context of our studies aimed for the development of ketenimine-participated synthetic methods,[11] we have focused on the reaction of 2-azido-2,4-dienoates and α-diazocarbonyl compounds. When the solution of ethyl 2-azido-5-phenylpenta-2,4-dienoate (**1a**), 2-diazo-1-phenylethanone (**2a**), and triphenylphosphine in toluene was refluxed for 10 h, ethyl 6-benzyl-5-phenylpicolinate (**3a**) was produced in 10% yield. In an attempt to improve the yield, subsequent work focused on optimization of the reaction conditions. We then examined the reaction temperature and several other solvents such as xylene, tetrahydrofuran, 1,2-dichloroethane, and CH_3CN. The best yield (80%) was obtained when the reaction was performed in xylene at 140 °C for 2 h (Table 1, entry 1).

With the suitable reaction conditions in hand, we examined the scope of this process using various 2-azido-2,4-dienoates **1**[12] and α-diazoketones **2**.[13] As shown in Table 1, all of the reactions generated pyridines **3** in good yields (70−90%). Furthermore, the electron-rich azides (Table 1, entries 11−14)

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(4) For the synthesis of substituted pyridines via multicomponent reactions, see recent examples: (a) Sasada, T.; Sakai, N.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 6905–6908. (b) Senaiar, R. S.; Young, D. D.; Deiter, A. *Chem. Commun.* **2006**, 1313–1315. (c) Evdokimov, N.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899–902. (d) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541–5544. (e) Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152–3154. (f) Zhu, S.-L.; Ji, S.-J.; Su, X.-M.; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 1777–1781.

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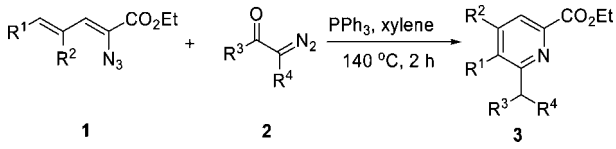
TABLE 1. Synthesis of Pyridines 3[a]



1 2 3

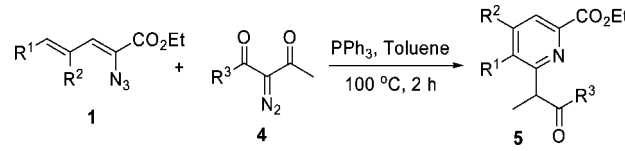
entry	R^1/R^2	R^3/R^4	product	yield (%)[b]
1	Ph/H (**1a**)	Ph/H (**2a**)	**3a**	80
2	Ph/H (**1a**)	4-MeC$_6$H$_4$/H (**2b**)	**3b**	81
3	Ph/H (**1a**)	4-BrC$_6$H$_4$/H (**2c**)	**3c**	78
4	Ph/H (**1a**)	4-MeOC$_6$H$_4$/H (**2d**)	**3d**	85
5	Ph/H (**1a**)	4-NO$_2$C$_6$H$_4$/H (**2e**)	**3e**	73
6	Ph/Me (**1b**)	4-BrC$_6$H$_4$/H (**2c**)	**3f**	81
7	Ph/Me (**1b**)	4-MeOC$_6$H$_4$/H (**2d**)	**3g**	86
8	2-ClC$_6$H$_4$/H (**1c**)	4-MeC$_6$H$_4$/H (**2b**)	**3h**	82
9	2-ClC$_6$H$_4$/H (**1c**)	4-BrC$_6$H$_4$/H (**2c**)	**3i**	80
10	2-ClC$_6$H$_4$/H (**1c**)	4-MeOC$_6$H$_4$/H (**2d**)	**3j**	83
11	2-MeOC$_6$H$_4$/H (**1d**)	Ph/H (**2a**)	**3k**	86
12	2-MeOC$_6$H$_4$/H (**1d**)	4-MeC$_6$H$_4$/H (**2b**)	**3l**	85
13	2-MeOC$_6$H$_4$/H (**1d**)	4-MeOC$_6$H$_4$/H (**2d**)	**3m**	90
14	2-MeOC$_6$H$_4$/H (**1d**)	4-NO$_2$C$_6$H$_4$/H (**2e**)	**3n**	76
15	2-NO$_2$C$_6$H$_4$/H (**1e**)	Ph/H (**2a**)	**3o**	72
16	2-NO$_2$C$_6$H$_4$/H (**1e**)	4-BrC$_6$H$_4$/H (**2c**)	**3p**	74
17	2-NO$_2$C$_6$H$_4$/H (**1e**)	4-MeOC$_6$H$_4$/H (**2d**)	**3q**	77
18	2-NO$_2$C$_6$H$_4$/H (**1e**)	4-NO$_2$C$_6$H$_4$/H (**2e**)	**3r**	70
19	 /H (**1f**)	Ph/H (**2a**)	**3s**	78
20	Ph/H (**1a**)	Me/CO$_2$Et (**2f**)	**3t**	82
21	Me/H (**1g**)	Me/CO$_2$Et (**2f**)	**3u**	77
22	Me/H (**1g**)	Ph/H (**2a**)	**3v**	78

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), PPh$_3$ (0.5 mmol), xylene (20 mL), N$_2$, 140 °C, 2 h. [b] The yield of the isolated product.

gave better yields than the electron-deficient azides (Table 1, entries 8−10 and 15−18).

Next, our attention was directed toward the reaction of 2-diazo-1,3-diones **4**[14] (Table 2). It was found that all the reactions could take place at lower temperature (100 °C) in toluene, resulting in pyridines **5** in good yields (76−85%). In all cases, pyridines **5** were isolated as the sole product. Herein we described our working hypothesis of the mechanism in Scheme 1. First, azide **1** reacts with triphenylphosphine to form phosphazene **A** via the Staudinger−Meyer reaction,[15] while α-diazoketone **2** transforms to ketene **B** through the Wolff rearrangement reaction.[16] Then the aza-Wittig reaction between phosphazene **A** and ketene **B** affords *N*-vinylic ketenemine **C**.[17] Finally, the electrocyclic ring closure of **C** and a subsequent double bond isomerization give pyridine **3**.

TABLE 2. Synthesis of Pyridines 5[a]

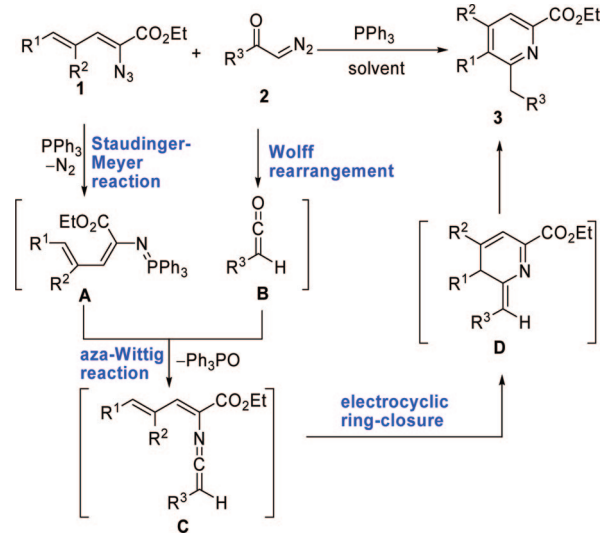


1 4 5

entry	R^1/R^2	R^3	product	yield (%)[b]
1	Ph/H (**1a**)	Ph (**4a**)	**5a**	78
2	Ph/H (**1a**)	4-BrC$_6$H$_4$ (**4c**)	**5b**	77
3	Ph/Me (**1b**)	Ph (**4a**)	**5c**	79
4	Ph/Me (**1b**)	4-MeC$_6$H$_4$ (**4b**)	**5d**	81
5	Ph/Me (**1b**)	4-BrC$_6$H$_4$ (**4c**)	**5e**	76
6	Ph/Me (**1b**)	4-MeOC$_6$H$_4$ (**4d**)	**5f**	85
7	Ph/H (**1a**)	Me (**4e**)	**5g**	80

[a] Reaction conditions: **1** (0.5 mmol), **4** (0.5 mmol), PPh$_3$ (0.5 mmol), toluene (20 mL), N$_2$, 100 °C, 2 h. [b] The yield of the isolated product.

SCHEME 1. A Plausible Mechanism for the Synthesis of Pyridines



In summary, we have demonstrated an efficient synthesis of substituted pyridines via a one-pot cascade reaction of 2-azido-2,4-dienoates, α-diazocarbonyl compounds, and triphenylphosphine. The procedure is rapid and general, and the substrates are readily available.[12,13,18] This methodology will find applications in the synthesis of natural products and organic materials as well as ligands.

Experiment Section

General Procedure for the Synthesis of Pyridines 3. To a solution of PPh$_3$ (0.131 g, 0.5 mmol) in anhydrous xylene (10 mL)

(13) α-Diazoketones were prepared by the reaction of acetophenones with 2,2,2-trifluoroethyl trifluoroacetate in the presence of LiHMDS and then treating with MsN_3/Et$_3$N. For the method, see: Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.

(14) 2-Diazo-1,3-diones were prepared from 1,3-diones and *p*-toluenesulfonyl azide. For the method, see: Regitz, C. J. *Chem. Ber.* **1966**, *99*, 3128–3147.

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(18) Many azides have hazardous behavior and some of them are potential energetic materials (see: Badgujar, D. M.; Talawar, M. B.; Asthana, S. N.; Mahulikar, P. P. *J. Hazard. Mater.* **2008**, *151*, 289–305.). Although we did not encounter any danger in our experiment, the caution about the potential hazardous behavior of azides should be indicated.

was added dropwise a solution of **1** (0.5 mmol) and **2** (0.5 mmol) in anhydrous xylene (10 mL) at 140 °C under nitrogen atmosphere over 30 min. The mixture was stirred for 2 h. The solvent was evaporated in vacuum and residual oil was purified by silica gel column chromatography, using hexane/EtOAc (5:1) as the eluent, to afford pure **3**.

Ethyl 6-benzyl-5-phenylpicolinate (3a): yellow oil; IR (KBr) 1741, 1495, 1445, 1386, 1137, 1007, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, $J = 7.8$ Hz, 1 H), 7.63 (d, $J = 7.8$ Hz, 1 H), 7.38−7.36 (m, 3 H), 7.15−7.09 (m, 5 H), 6.96 (d, $J = 6.8$ Hz, 2 H), 4.50 (q, $J = 7.1$, 2 H), 4.26 (s, 2 H), 1.45 (t, $J = 7.1$, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 158.7, 147.0, 141.1, 139.5, 139.0, 138.8, 129.1, 129.0, 128.6, 128.3, 128.2, 126.2, 123.1, 62.0, 42.1, 14.6 ppm; MS (ESI) *m*/*z* ($[M + H]^+$) 318. Anal. Calcd for $C_{21}H_{19}NO_2$: C 79.47, H 6.03, N 4.41. Found: C 79.40, H 6.03, N 4.43.

Ethyl 6-(4-methylbenzyl)-5-phenylpicolinate (3b): yellow oil; IR (KBr) 1742, 1513, 1444, 1384, 1137, 1007, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, $J = 7.9$ Hz, 1 H), 7.62 (d, $J = 7.8$ Hz, 1 H), 7.39−7.38 (m, 3 H), 7.17−7.15 (m, 2 H), 6.95 (d, $J = 7.9$ Hz, 2 H), 6.87 (d, $J = 8.0$ Hz, 2 H), 4.49 (q, $J = 7.1$ Hz, 2 H), 4.20 (s, 2 H), 2.25 (s, 3 H), 1.45 (t, $J = 7.1$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 158.9, 147.0, 141.0, 139.1, 138.7, 136.5, 135.6, 129.2, 129.0, 128.9, 128.6, 128.2, 123.0, 62.0, 41.6, 21.2, 14.6 ppm; MS (ESI) *m*/*z* ($[M + H]^+$) 332. Anal. Calcd for $C_{22}H_{21}NO_2$: C 79.73, H 6.39, N 4.23. Found: C 79.73, H 6.37, N 4.24.

General Procedure for the Synthesis of 5. To a solution of PPh_3 (0.131 g, 0.5 mmol) in anhydrous toluene (10 mL) was added dropwise a solution of **1** (0.5 mmol) and **4** (0.5 mmol) in anhydrous toluene (10 mL) under nitrogen atmosphere at 100 °C over 30 min. After the mixture was stirred for 2 h, the solvent was evaporated in vacuum and residual oil was purified by silica gel column chromatography, using hexane/EtOAc (5:1) as the eluent, to afford pure **5**.

Ethyl 6-(1-oxo-1-phenylpropan-2-yl)-5-phenylpicolinate (5a): yellow oil; IR (KBr) 1742, 1716, 1447, 1387, 1143, 1006, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.9$ Hz, 1 H), 7.63 (d, $J = 7.9$ Hz, 1 H), 7.59−7.57 (m, 2 H), 7.43−7.39 (m, 4 H), 7.30−7.26 (m, 4 H), 4.91−4.89 (m, 1 H), 4.43−4.39 (m, 2 H), 1.64 (d, $J = 6.9$ Hz, 3 H), 1.40 (t, $J = 7.1$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 165.5, 158.6, 147.5, 140.2, 138.7, 137.1, 132.5, 129.1, 129.0, 128.6, 128.4, 128.3, 123.1, 61.8, 47.6, 17.3, 14.5 ppm; MS (ESI) *m*/*z* ($[M + H]^+$) 360. Anal. Calcd for $C_{23}H_{21}NO_3$: C 76.86, H 5.89, N 3.90. Found: C 76.89, H 5.92, N 3.93.

Ethyl 6-(1-(4-bromophenyl)-1-oxopropan-2-yl)-5-phenylpicolinate (5b): white solid, mp 90−91 °C; IR (KBr) 1743, 1710, 1443, 1387, 1140, 1007, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J = 7.8$ Hz, 1 H), 7.65 (d, $J = 7.9$ Hz, 1 H), 7.46−7.40 (m, 7 H), 7.30−7.27 (m, 2 H), 4.82 (q, $J = 6.9$ Hz, 1 H), 4.43−4.38 (m, 2 H), 1.63 (d, $J = 6.9$ Hz, 3 H), 1.40 (t, $J = 7.1$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 165.3, 158.3, 147.6, 140.1, 138.9, 138.5, 135.9, 131.7, 129.9, 129.1, 128.7, 127.4, 123.3, 61.8, 47.7, 17.3, 14.5 ppm; MS (ESI) *m*/*z* ($[M + H]^+$) 438. Anal. Calcd for $C_{23}H_{20}BrNO_3$: C 63.02, H 4.60, N 3.20. Found: C 63.01, H 4.66, N 3.20.

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Supporting Information Available: Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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