NOVEL PYRIDINE–FORMATION REACTIONS of 2–(PHOSPHORANYLIDENEAMINO)ACRYLALDEHYDES WITH ACETYLENIC ESTERS. SYNTHESIS OF 2–MONO– AND 2,5–DISUBSTITUTED NICOTINATES

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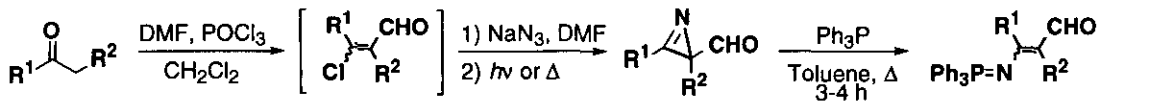
Abstract – Preparation of 2–(phosphoranylideneamino)acrylaldehydes, novel formyl–substituted (vinylimino)phosphoranes, was accomplished by the reaction of formyl–*2H*–azirines with triphenylphosphine. Their novel pyridine–formation reactions with acetylenic esters achieved the preferential formation of 2–mono– and 2,5–disubstituted nicotinate derivatives.

Preparation of substituted nicotinates is worth being investigated to provide the facile and versatile synthetic methods of simple but important pyridine derivatives and to explore their synthetic application to highly functional molecules. Recently iminophosphoranes[2] have been studied extensively as versatile tools in heterocyclic chemistry and (vinylimino)phosphoranes,[2b] primary enamine equivalents, have been shown to be useful synthetic synthons for various heteroaromatic compounds including such pyridine[3a] and nicotinate[3b] derivatives. We have previously reported the synthesis of chiral bridged NADH models, biomimetic reducing agents with remarkably high enantioselectivity and stereospecificity, from a bridged nicotinate having a [10](2,5)pyridinophane (parapyridinophane) skeleton by the reaction of 2–(phosphoranylideneamino)cyclododecene–1–carboxaldehyde with methyl propiolate.[4] Along with our studies on development of novel synthetic methods for various pyridine derivatives, we have investigated the reactivity and synthetic utility of various 2–(phosphoranylideneamino)acrylaldehydes, formyl–substituted (vinylimino)phosphoranes, as the precursors for more generally substituted nicotinate derivatives. In this paper, we describe the preparation of several alkyl and/or phenyl substituted 2–(phosphoranylideneamino)acrylaldehydes (**3a–d**) from formyl–substituted azirines (**2a–d**) and their reactions with acetylenic esters as unique synthetic approaches to 2–mono and 2,5–disubstituted nicotinate derivatives.



1a: 76%
1c: 62% (85%)
1d: 69% (96%)
conversion yields in parentheses

2a: 51%
2b: ref. 8.
2c: 53%
2d: 69%

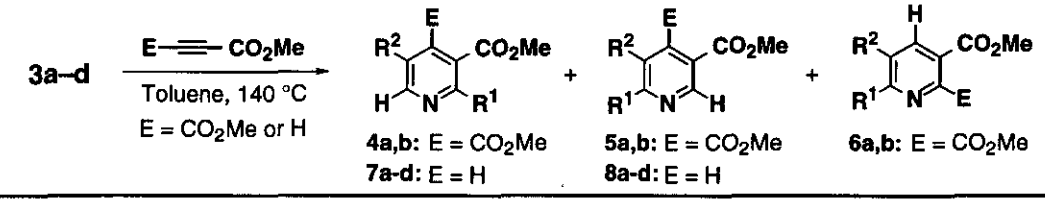
3a: 91% (*E*)
3b: 94% (*E*/*Z* = 92/8)
3c: 84% (*E*/*Z* = 92/8)
3d: 71% (*E*/*Z* = 92/8)

Scheme 1 **a**: R^1 = Ph, R^2 = Me; **b**: R^1 = Ph, R^2 = H; **c**: R^1 = *n*-Pr, R^2 = Et; **d**: R^1 = *n*-Bu, R^2 = *n*-Pr

Preparation of the iminophosphoranes (**3a–d**) is shown in Scheme 1. Vilsmeier–Haack formylation[5] of propiophenone, 4–heptanone, and 5–nonanone afforded the corresponding 2–chloroacrylaldehydes (**1a**,[6] **1c**, and **1d**), respectively, and the substitution reactions with NaN_3 gave the *trans*–azides and formyl–*2H*–azirines (**2a**,[7] **2c**, and **2d**), the latter of which was formed by ring closure reactions after spontaneous denitrogenation of the *cis*–azides at room temperature. The following thermal or photochemical reactions of the mixtures transformed the remaining *trans*–azides to provide **2a,c,d**. 3–Phenyl–2–methyl–*2H*–azirine–2–carboxaldehyde (**2b**) was prepared independently according to the known procedure.[8] The reaction of **2a–d** with PPh_3 (1.0 eq.) in refluxing toluene effected the ring–opening of azirine to afford **3a–d** in good yields.[9] The structures of **3a–d** were deduced from their NMR and MS spectral data. The NOE enhancement was observed clearly between the formyl and the R^1 protons (6% for aromatic protons of **3a,b** and 15% for allylic protons of **3c,d**), which shows that the configuration of the C–C double bonds of their major isomers is proven to be *E*–form though the compounds (**3b–d**) contain small amounts of their *Z*–isomers in a ratio of 92/8. The ring–opening reactions require a formyl group to activate an azirine ring. Indeed, the dimethyl acetal derivative of **2b**[6] did not react with PPh_3 under the same reaction conditions employed for **2b**. The present method for the preparation of **3a–d** from **2a–d** provides an alternative route to some class of (vinylimino)phosphoranes with electron withdrawing groups when the corresponding vinyl azides are not available for Staudinger reactions because of their instability.

Table 1 summarizes the reactions of **3a–d** with acetylenic esters. The reaction of **3a,b** with two equivalent of dimethyl acetylenedicarboxlate (DMAD) was carried out in toluene at 140 °C in autoclave (Runs 1 and 2). As for the reaction of **3a**, pyridine derivatives of **4a**, **5a**,[10] and **6a** were obtained in 45%, 10%, and 15% yields, respectively (Run 1). In the case of **3b**, the yield of the major product (**4b**) increased to 55%, and **5b**[11] and **6b**[12] were obtained in 9% and 2% yields, respectively (Run 2). The reaction of **3a–d** with 10 equivalents of methyl propiolate (MP) afforded also the corresponding nicotinate derivatives (**7a–d** and **8a,c,d**) under the same reaction conditions (Runs 3–6). The major products (**7a–d**) are the same type of substituted pyridines as **4a,b**. The isomers (**8a**),[13] (**8c**), and (**8d**) resulted in much lower yields and none

Table 1 Reaction of **3a–d** with Acetylenic Esters

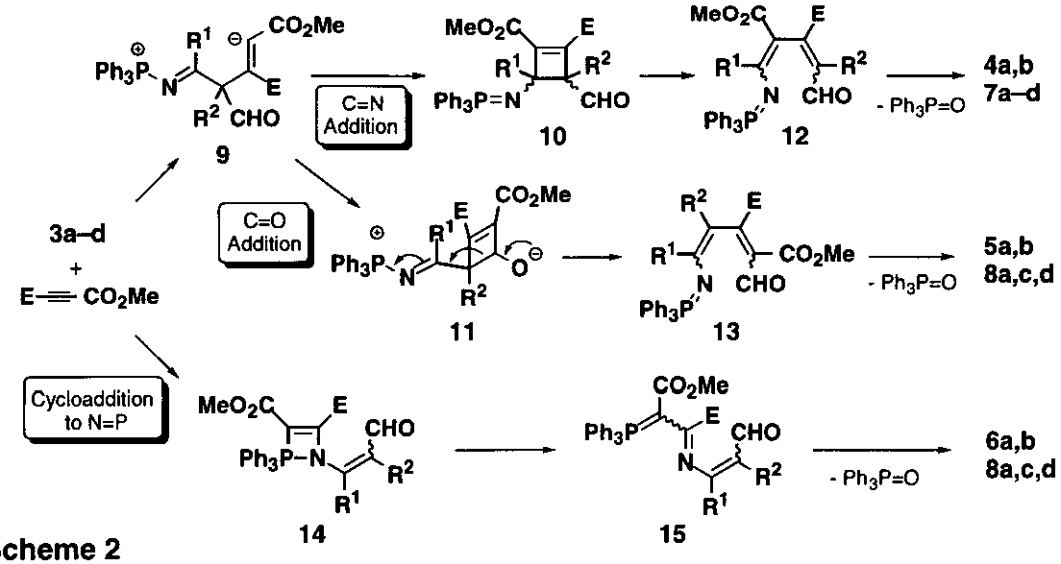


Run	3	R^1	R^2	Acetylene[a]	E	Product (Yields)			Total Yields
1	**3a**	Ph	Me	DMAD	CO_2Me	**4a** (45%)	**5a**(10%)	**6a** (15%)	70%
2	**3b**	Ph	H	DMAD	CO_2Me	**4b** (55%)	**5b** (9%)	**6b** (2%)	66%
3	**3a**	Ph	Me	MP	H	**7a** (44%)	**8a** (4%)		48%
4	**3b**	Ph	H	MP	H	**7b** (37%)	**8b** --		37%
5	**3c**	*n*–Pr	Et	MP	H	**7c** (49%)	**8c** (4%)		53%
6	**3d**	*n*–Bu	*n*–Pr	MP	H	**7d** (35%)	**8d** (4%)		39%

a) DMAD: dimethyl acetylenedicarboxylate; MP: methyl propiolate.

of **8b**[14] was obtained in the reaction. The 2–(phosphoranylideneamino)acrylaldehydes (**3a–d**) require higher temperatures to react with acetylenic esters rather than other (vinylimino)phosphoranes[15] according to the incorporation of the electron withdrawing formyl groups. The structures of the pyridine derivatives thus obtained were determined by ^{1}H NMR and MS spectral data. The aromatic protons of **4a, 5a,** and **6a** appear at δ 8.65, δ 9.13, and δ 8.09 ppm, respectively, and are assigned to 6–, 2–, and 4–positions on each pyridine ring. The down–field shift of the aromatic proton of **5a** as compared to that of **4a** is attributable to an anisotropy effect of the neighboring carbonyl group. As for compounds (**4b–6b**) (R^2 = H), the coupling constants of the two aromatic protons are informative (J = 5.1, 0, and 8.5 Hz, respectively), indicating that these protons are at α,β–, α,δ–, and β,γ–positions of **4b–6b**, respectively. The structures of nicotinates (**7** and **8**) were also assigned similarly.

The postulated pathways for the formation of pyridine derivatives are depicted in Scheme 2. Enamine–type addition[16] of **3a–d** to the β–position of acetylenic esters forms ionic intermediates (**9**) followed by C=N and C=O additions to produce cyclobutene intermediates (**10**[17] and **11**), respectively. The spontaneous ring–opening reactions of **10** and **11** generate dienyl aldehydes (**12**[17] and **13**) which undergo intramolecular aza–Wittig reactions to give **4/7** and **5/8**. The formation of **6** and a portion of **8** was best rationalized by the cycloaddition[17] of acetylenic esters to N=P double bond of **3a–d** to give intermediates (**14**). The following cycloreversion of **14** and the successive intramolecular Wittig reaction of **15** afford **6** and **8**. The formation of nicotinate derivatives (**4a,b** and **7a–d**) as major products indicates that 2–(phosphoranylideneamino)acrylaldehydes (**3a–d**) react with acetylenic esters as enamine equivalent reagents since enamine–like [2+2] cycloaddition of **3a–d** giving **10** occurs predominantly. These novel pyridine–formation reactions provide a convenient method for the syntheses of 2–mono and 2,5–disubstituted nicotinate derivatives. Especially, the latter nicotinates such as **7a–d** could be useful synthetic intermediates for reference molecules of our highly functional bridged NADH models.



Scheme 2

EXPERIMENTAL

General. NMR spectra were recorded on JEOL JNM–GSX500, JNM–AL300, or JNM–EX270 spectrometer. Chemical shifts are reported in ppm relative to Me_4Si for ^1H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standard. Unless otherwise specified, NMR spectra were measured in $CDCl_3$ at ambient temperature: ^1H NMR spectra at 300 MHz; ^{13}C NMR spectra at 75.5 MHz. MS spectra were recorded on JEOL JMS–HX110 or JEOL JMS–SX102 spectrometer. Flash chromatography was performed using Silica gel FL60D (Fuji Silysia Chemical Ltd.) unless otherwise specified. Thin layer chromatography was performed using Merck aluminum oxide 60 F_{254} glass plates (Art. 5713, 0.25 mm thick). Melting points were recorded on Yanagimoto apparatus and are uncorrected.

3–Phenyl–*2H*–azirine–2–carboxaldehyde (2a). 2–Chloro–1–methylcinnamaldehyde (**1a**) (bp 93 °C, 0.17 Torr) was prepared by Vilsmeier–Haack formylation of propiophenone in 76% yield according to the similar procedure described in literature.[6] A solution of 2–chloro–1–methylcinnamaldehyde (902.5 mg, 5.00 mmol) and NaN_3 (490 mg, 7.50 mmol) in DMF (5 mL) was stirred at rt for 12 h. Water was added and the mixture was extracted with ether (3x). The combined ethereal layer was washed with water (3x) and brine (1x) and dried over $MgSO_4$. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel to give a mixture of the corresponding azide and **2a** in a 88/12 ratio (467 mg, 51%). The mixture (441 mg, 2.36 mmol) was heated at reflux in chloroform (20 mL) for 12 h and, after removal of solvent *in vacuo*, the residue was purified by short path distillation (60 °C, 0.01 Torr) to give **2a** (299 mg, 80%): oil; ^1H NMR (500 MHz) δ 1.52 (s, 3H), 7.61 (t, J = 8.1, 7.3 Hz, 2H), 7.69 (tt, J = 7.3, 1.3 Hz, 1H), 7.86 (2H, J = 8.1, 1.3 Hz, 2H), 8.85 (s, 1H). The compound (**2a**) was previously reported in literature.[7]

Formyl–*2H*–azirines (2c,d). *Representative procedure.* To a solution of DMF (1.16 mL, 15.0 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C a solution of $POCl_3$ (1.40 mL, 15.0 mmol) in CH_2Cl_2 (2.5 mL), and the mixture was stirred at rt for 30 min. A solution of 5–nonanone (711 mg, 5.0 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise at 0°C and the solution was stirred at 10 °C for 24 h. The reaction mixture was then poured onto ice and was stirred at rt until the exothermic hydrolysis was complete. The mixture was extracted with ether (2x) and the combined ethereal layer was washed with small portions of water (1x) and brine (1x), dried over $MgSO_4$, and concentrated *in vacuo* to give a crude mixture (911 mg) of the corresponding chloroenal (**1d**) and recovered 5–nonanone. A solution of the mixture in DMF (5 mL) was stirred with NaN_3 (325 mg, 5.0 mmol) at rt for 4 h. Water was added and the mixture was extracted with ether (2x). The combined ethereal layer was washed with water (2x) and brine (1x) and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the residue was dissolved in CH_3CN (25 mL) and was irradiated with sun–lamp (λmax = 365 nm) through Pyrex filter at rt for 6 h. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel by using ether–hexane (1/5) to give **2d** (399 mg, 48% from 5–nonanone). The yields are summarized in Scheme 1.

2c: oil; ^1H NMR δ 0.81 (t, J = 7.5 Hz, 3H), 1.09 (dd, J = 7.5, 7.3 Hz, 3H), 1.81 (dq, J = 14.7, 7.3 Hz, 1H), 1.82 (ddt, J = 7.4, 7.2, 7.5 Hz, 2H), 1.96 (dq, J = 14.9, 7.5 Hz, 1H), 2.83 (dt, J = 16.7, 7.2 Hz,

1H), 2.85 (dt, J = 16.7, 7.4 Hz, 1H), 8.75 (s, 1H); MS (EI) m/z (%) 139 (11) [M$^+$], 111 (100); HRMS (EI) calcd for $C_8H_{13}NO$ 139.0997, found 139.1001.

2d: oil; ^{1}H NMR δ 0.89 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H), 1.23 (sex, J = 7.5 Hz, 2H), 1.48 (sex, J = 7.5 Hz, 2H), 1.67–1.80 (m, 3H), 1.86 (dt, J = 15.0, 7.5 Hz, 1H), 2.80 (dt, J = 16.9, 7.5 Hz, 1H), 2.88 (dt, J = 16.9, 7.5 Hz, 1H), 8.74 (s, 1H); ^{13}C NMR δ 13.6, 13.9, 18.5, 22.3, 26.3, 27.7, 30.1, 49.0, 167.8, 200.7; MS (EI) m/z (%) 167 (11) [M$^+$], 125 (100); HRMS (EI) calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1308.

2–(Phosphoranylideneamino)acrylaldehydes (3a–d). *Representative procedure.* A solution of **2a–d** (18.8 mmol) and PPh_3 (5.03 g, 19.2 mmol) in toluene (20 mL) was heated at reflux for 3 h. After the reaction mixture was concentrated *in vacuo*, yellow solid precipitated in ether was filtered to give **3a–d**. The yields are listed in Scheme 1.

3a (*E*): mp 168–170 °C (from toluene); ^{1}H NMR (500 MHz) δ 2.23 (s, 3H), 6.74 (dd, J = 7.3, 1.7 Hz, 2H), 6.77 (dd, J = 7.7, 7.3 Hz, 2H), 6.93 (tt, J = 7.3, 1.7 Hz, 1H), 7.36 (ddd, J_{H-H} = 8.1, 7.7 Hz, J_{H-P} = 3.4 Hz, 6H), 7.49 (ttd, J_{H-H} = 7.7, 1.3 Hz, J_{H-P} = 1.7 Hz, 3H), 7.52 (ddd, J_{H-H} = 8.1, 1.3 Hz, J_{H-P} = 12.4 Hz, 6H), 8.99 (s, 1H); ^{13}C NMR δ 9.9, 122.1 (d, J_{P-C} = 20.6 Hz), 127.0, 127.2 (2C), 128.5 (d, J_{P-C} = 12.5 Hz, 6C), 128.6 (2C), 130.1 (d, J_{P-C} = 101.5 Hz, 3C), 131.8, (d, J_{P-C} = 3.1 Hz, 3C), 132.3, (d, J_{P-C} = 10.0 Hz, 6C), 139.3 (d, J_{P-C} = 8.1 Hz), 171.6 (d, J_{P-C} = 1.9 Hz), 191.9 (d, J_{P-C} = 3.7 Hz); MS (EI) m/z (%) 421 (29) [M$^+$], 262 (100); HRMS (EI) calcd for $C_{28}H_{24}NOP$ 421.1595, found 421.1604. Anal. Calcd for $C_{28}H_{24}NOP$: C, 79.79; H, 5.74; N, 3.32. Found: C, 79.73; H, 5.83; N, 3.31.

3b (*E*/*Z* = 92/8): mp 89–103 °C (decomp) (from toluene); ^{1}H NMR δ 5.34 (dd, J_{H-H} = 8.8 Hz, J_{P-H} = 1.2 Hz, 1H, *E*), 5.63 (dd, J_{H-H} = 8.6 Hz, J_{P-H} = 3.5 Hz, 1H, *Z*), 6.96 (dd, J = 7.7, 7.3 Hz, 2H, *Z*), 7.08 (t, J = 7.3 Hz, 1H, *Z*), 7.19 (d, J = 7.7 Hz, 2H, *Z*), 7.32–7.43 (m, 3H, *E*), 7.49 (dddd, J_{H-H} = 6.9, 6.1, 1.5 Hz, J_{P-H} = 3.2 Hz, 6H, *E*), 7.54–7.65 (m, 5H, *E*), 7.74 (dddd, J_{H-H} = 6.9, 2.0, 1.5 Hz, J_{P-H} = 12.2 Hz, 6H, *E*), 9.10 (d, J = 8.8 Hz, 1H, *E*), 10.25 (d, J = 8.6 Hz, 1H, *Z*) and the other signals for *Z*–form (15H) are hidden behind those of (*E*)–form; ^{13}C NMR (*E*–form) δ 112.7, 127.6 (2C), 127.7 (d, J_{P-C} = 100.3 Hz, 3C), 128.96, 128.98 (d, J_{P-C} = 11.8 Hz, 6C,), 129.6 (2C), 132.5 (3C), 132.7, (d, J_{P-C} = 10.0 Hz, 6C), 141.5 (d, J_{P-C} = 23.7 Hz), 175.1 (d, J_{P-C} = 4.4 Hz), 191.8; MS (EI) m/z (%) 407 (24) [M$^+$], 262 (100); HRMS (EI) calcd for $C_{27}H_{22}NOP$ 407.1439, found 407.1444. Anal. Calcd for $C_{27}H_{22}NOP$: C, 79.59; H, 5.44; N, 3.44. Found: C, 79.95; H, 5.64; N, 3.18.

3c (*E*/*Z* = 92/8): white solid; mp 164–166 °C (from toluene); ^{1}H NMR δ 0.39 (t, J = 7.3 Hz, 3H, *E*), 1.09 (t, J = 7.3 Hz, 3H, *E*), 1.13 (dtd, J = 10.4, 7.3, 5.9, 2H, *E*), 2.29 (AA'XX', J = 10.4, 5.9 Hz, 2H, *E*), 2.64 (q, J = 7.3 Hz, 2H, *E*), 7.50 (dddd, J_{H-H} = 7.7, 7.0, 1.6 Hz, J_{P-H} = 3.1 Hz, 6H, *E*), 7.58 (ttd, J_{H-H} = 7.7, 1.6 Hz, J_{H-P} = 1.3 Hz, 3H, *E*), 7.72 (dtd, J_{H-H} = 7.0, 1.6 Hz, J_{P-H} = 12.3 Hz, 6H, *E*), 9.78 (s, 1H, *E*), 10.63 (s, 1H, *Z*) and the other signals for Z–form (12H) are hidden behind those of (*E*)–form; ^{13}C NMR (*E*–form) δ 13.5, 13.6, 17.9, 24.5, 36.8 (d, J_{P-C} = 8.7 Hz), 126.1 (d, J_{P-C} = 21.2 Hz), 128.8 (d, J_{P-C} = 12.5 Hz, 6C), 130.6 (d, J_{P-C} = 101.5 Hz, 3C), 132.2 (d, J_{P-C} = 3.1 Hz, 3C), 132.4 (d, J_{P-C} = 10.6 Hz, 6C), 171.8, 187.4 (d, J_{P-C} = 3.7 Hz); MS (EI) m/z (%) 401 (22) [M$^+$], 262 (100); HRMS

(EI) calcd for $C_{26}H_{28}NOP$ 401.1908, found 401.1912. Anal. Calcd for $C_{26}H_{28}NOP$: C, 77.78; H, 7.03; N, 3.49. Found: C, 78.08; H, 6.97; N, 3.20.

3d (*E*/*Z* = 92/8): white solid; mp 146–148 °C (from toluene); ^{1}H NMR δ 0.54 (t, J = 7.3 Hz, 3H, *E*–Bu), 0.73 (sex, J = 7.3 Hz, 2H, *E*–Bu), 0.99 (t, J = 7.3 Hz, 3H, *E*–Pr), 1.07 (dtd, J = 11.3, 7.3, 5.0 Hz, 2H, *E*–Bu), 1.41 (sex, J = 6.8 Hz, 2H, *Z*), 1.54 (dtd, J = 10.1, 7.3, 5.7 Hz, 2H, *E*–Pr), 2.06 (t, J = 7.9 Hz, 2H, *Z*), 2.19 (t, J = 7.8 Hz, 2H, *Z*) 2.35 (AA'XX', J = 11.4, 5.1 Hz, 2H, *E*–Bu), 2.60 (AA'XX', J = 10.1, 5.7 Hz, 2H, *E*–Pr), 7.49 (dddd, J_{H-H} = 7.7, 7.0, 1.6 Hz, J_{P-H} = 3.1 Hz, 6H, *E*), 7.55 (ttd, J_{H-H} = 7.7, 1.6 Hz, J_{H-P} = 1.5 Hz, 3H, *E*), 7.73 (dtd, J_{H-H} = 7.0, 1.6 Hz, J_{P-H} = 12.3 Hz, 6H, *E*), 9.80 (s, 1H, *E*), 10.65 (s, 1H, *Z*) and the other signals for *Z*-form (10H) are hidden behind those of (*E*)–form; ^{13}C NMR (67.8 MHz, *E*–form) δ 13.6, 14.7, 22.1, 22.6, 27.0, 33.6, 35.3 (d, J_{P-C} = 8.9 Hz), 124.3 (d, J_{P-C} = 21.2 Hz), 128.7 (d, J_{P-C} = 12.3 Hz, 6C), 130.6 (d, J_{P-C} = 101.7 Hz, 3C), 132.1 (d, J_{P-C} = 2.8 Hz, 3C), 132.3 (d, J_{P-C} = 10.1 Hz, 6C), 172.2, 187.5 (d, J_{P-C} = 4.5 Hz); MS (EI) *m/z* (%) 429 (20) [M$^+$], 262 (100); HRMS (EI) calcd for $C_{28}H_{32}NOP$ 429.2221, found 429.2233. Anal. Calcd for $C_{28}H_{32}NOP$: C, 78.29; H, 7.51; N, 3.26. Found: C, 78.45; H, 7.51; N, 3.31.

The Reactions of 3a,b with DMAD. A solution of **3a,b** (5.05 mmol) and DMAD (4.3 mL, 51.5 mmol) in toluene (15 mL) was heated at 140 °C in an autoclave reactor for 12 h. The mixture was separated by flash chromatography on silica gel by using ether–hexane (1/5) or by TLC on aluminum oxide by using $CHCl_3$–hexane (1/2) to give **4a,b**, **5a,b** and **6a,b**. The compounds (**5a**, **5b**, and **6b**) were previously reported in literature.[10–12] The reaction conditions and yields are listed in Table 1.

4a: mp 102–103 °C (from ether); ^{1}H NMR (270 MHz) δ 2.45 (s, 3H), 3.66 (s, 3H), 3.93 (s, 3H), 7.35–7.60 (m, 5H), 8.65 (s, 1H); ^{13}C NMR (67.8 MHz) δ 16.7, 52.7, 52.9, 125.7, 128.1 (2C), 128.3 (2C), 128.8 (2C), 139.0, 139.5, 152.4, 155.4, 166.6, 168.1; MS (EI) *m/z* (%) 285 (51) [M$^+$], 270 (100); HRMS (EI) calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1002. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.39; H, 5.30; N, 4.91. Found: C, 67.14; H, 5.27; N, 4.90.

4b: mp 101–102 °C (from EtOH); ^{1}H NMR (500 MHz) δ 3.36 (s, 3H), 3.96 (s, 3H), 7.42–7.48 (m, 3H), 7.59–7.63 (m, 2H), 7.70 (d, J = 5.1 Hz, 1H), 8.87 (d, J = 5.1 Hz, 1H); ^{13}C NMR (126 MHz) δ 52.8, 53.2, 121.2, 128.40 (3C), 128.44 (2C), 129.2, 136.4, 138.6, 150.7, 157.4, 165.0, 168.2; MS (EI) *m/z* (%) 271 (30) [M$^+$], 256 (100); HRMS (EI) calcd for $C_{15}H_{13}NO_4$ 271.0844, found 271.0844. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.18; H, 4.87; N, 5.13.

6a: oil; ^{1}H NMR (270 MHz) δ 2.44 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 7.37–7.58 (m, 5H), 8.09 (s, 1H); MS (EI) *m/z* (%) 285 (100) [M$^+$]; HRMS (EI) calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1000.

The Reactions of 3a–d with MP. A solution of **3a–d** (5.05 mmol) and methyl propiolate (4.3 mL, 51.5 mmol) in toluene (15 mL) was heated at 140 °C in an autoclave reactor for 12 h. The mixture was separated by flash chromatography on silica gel by using ether–hexane (1/5) or by TLC on aluminum oxide by using ethyl acetate–hexane (1/9) to give **7a–d** and **8a,c,d**. The compound (**8a**) was previously reported in literature.[13] The reaction conditions and yields are listed in Table 1.

7a: oil; ^{1}H NMR (500 MHz) δ 2.43 (s, 3H), 3.69 (s, 3H), 7.38–7.45 (m, 3H), 7.52 (dd, J = 7.7, 1.3 Hz, 2H), 7.91 (d, J = 1.7 Hz, 1H), 8.61 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 17.9, 52.3, 126.4, 128.1 (2C), 128.4 (3C), 131.3, 138.2, 139.9, 151.8, 156.1, 168.7; MS (EI) *m/z* (%) 227 (28) [M$^+$], 212 (100); HRMS (EI) calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0953.

7b: oil; ^{1}H NMR (500 MHz) δ 3.70 (s, 3H), 7.35 (dd, J = 7.9, 5.1 Hz, 1H), 7.40–7.47 (m, 3H), 7.54 (dd, J = 7.7, 1.7 Hz, 2H), 8.10 (dd, J = 7.9, 1.7 Hz, 1H), 8.78 (dd, J = 5.1, 1.7 Hz, 1H); ^{13}C NMR (126 MHz) δ 52.4, 121.5, 127.0, 128.2 (2C), 128.5 (2C), 128.7, 137.9, 139.9, 151.3, 158.8, 168.6; MS (EI) *m/z* (%) 213 (24) [M$^+$], 198 (100); HRMS (EI) calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0797.

7c: oil; ^{1}H NMR δ 1.00 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.6 Hz, 3H), 1.73 (dtd, J = 9.6, 7.3, 6.0 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 3.09 (AA'XX', J = 9.6, 6.0 Hz, 2H), 3.92 (s, 3H), 7.97 (d, J = 2.0 Hz, 1H), 8.49(d, J = 2.0 Hz, 1H); ^{13}C NMR δ 14.2, 15.1, 23.3, 25.4, 38.5, 52.2, 124.9, 136.2, 137.6, 151.6, 160.6, 167.4; MS (EI) *m/z* (%) 207 (7) [M$^+$], 179 (100); HRMS (EI) calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1254.

7d: oil; ^{1}H NMR δ 0.94 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 1.42 (sex, J = 7.3 Hz, 2H), 1.66 (sex, J = 7.3 Hz, 2H), 1.67 (dtd, J = 9.9, 7.3, 5.5 Hz, 2H), 2.59 (t, J = 7.3 Hz, 2H), 3.11 (AA'XX', J = 9.9, 5.5 Hz, 2H), 3.91 (s, 3H), 7.94 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H); ^{13}C NMR δ 13.6, 13.9, 22.9, 24.1, 32.3, 34.3, 36.3, 52.2, 124.8, 134.7, 138.1, 152.0, 160.9, 167.4; MS (EI) *m/z* (%) 235 (3) [M$^+$], 193 (100); HRMS (EI) calcd for $C_{14}H_{21}NO_2$ 235.1572, found 235.1570.

8c: oil; ^{1}H NMR δ 1.01 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H), 1.76 (dtd, J = 9.7, 7.3, 5.9 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.83 (AA'XX', J = 9.7, 5.9 Hz, 2H), 3.92 (s, 3H), 8.05 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H); MS (EI) *m/z* (%) 207 (20) [M$^+$], 179 (100); HRMS (EI) calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1254.

8d: oil; ^{1}H NMR δ 0.96 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.43 (sex, J = 7.3 Hz, 2H), 1.61–1.72 (m, 4H) , 2.64 (AA'XX', J = 9.6, 6.2 Hz, 2H), 2.84 (AA'XX', J = 9.9, 5.6 Hz, 2H), 3.93 (s, 3H), 8.01 (d, J = 2.1 Hz, 1H), 8.96 (d, J = 2.1 Hz, 1H); MS (EI) *m/z* (%) 235 (8) [M$^+$], 193 (100); HRMS (EI) calcd for $C_{14}H_{21}NO_2$ 235.1572, found 235.1577.

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