# A Regioselective Synthesis of Dimethyl Phthalide-3-phosphonates[1]

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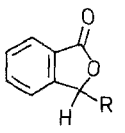
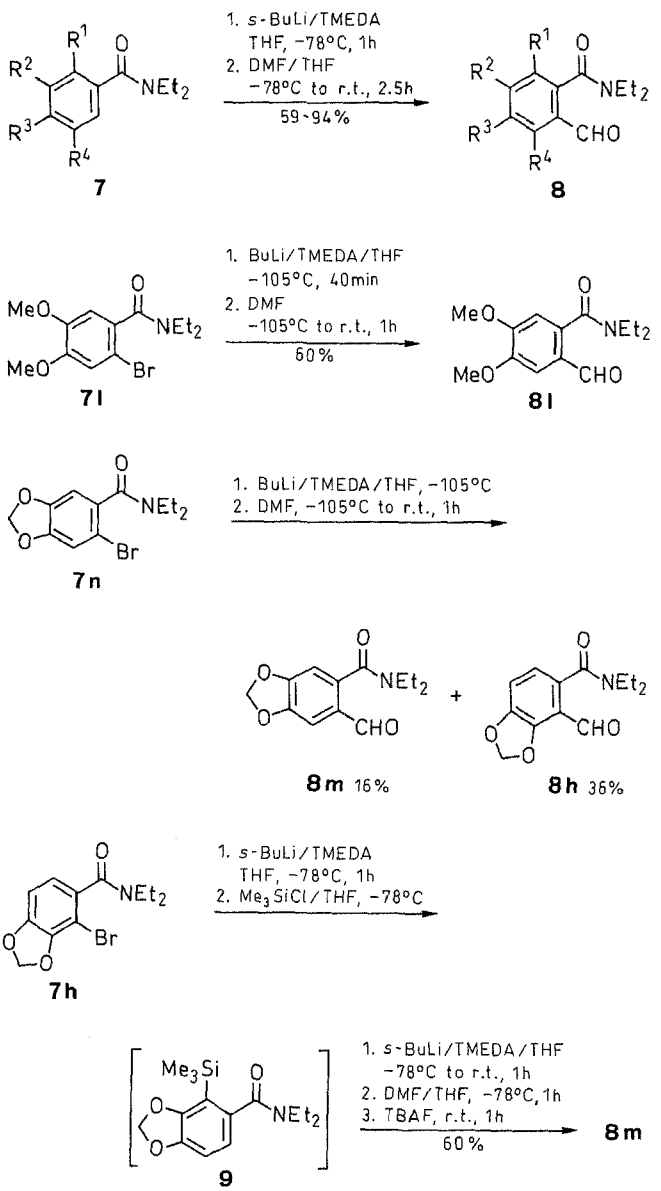
Dimethyl phthalide-3-phosphonates having various substituents on the benzene ring were regioselectively synthesized by the reaction of *N,N*-diethyl-2-formylbenzamides with *tert*-butyldimethylsilyl dimethyl phosphite followed by treatment with methanesulfonic acid. *N,N*-Diethyl-2-formylbenzamides were regioselectively prepared by ortho lithiation–formylation of the corresponding benzamides.

Phthalides are versatile compounds in organic synthesis.[2] Especially, organometallic derivatives of phthalide itself or 3-functionalized phthalides such as 3-cyano- **(1)**,[3] 3-phenylthio- **(2)**,[4] and 3-phenylsulfonylphthalide **(3)**[4] are useful for the regioselective annulation of aromatic rings. A common feature of these annulations is that metalated intermediates of phthalides undergo conjugated addition to electron-deficient olefines resulting in hydroquinone products. On the other hand, the utility of phthalide-3-phosphonates, **4**[5] and **5**[6], was briefly demonstrated for the syntheses of 3-alkylidene- and 3-benzylidenephthalides using the Wittig–Horner type reaction.[5,6] This synthetic method for ylidenephthalides is more advantageous than using the classical Perkin reaction of phthalic anhydrides with acid anhydrides or the Wittig reaction of triphenyl(3-phthalidyl)phosphonium bromide[7] with aldehydes. Moreover, Napolitano and Ramacciotti recently reported the transformation of dimethyl phthalide-3-phosphonates **5** into 3-substituted isocoumarins.[8]



| | R | | R |
|---|---|---|---|
| **1** | CN | **4** | $PO(OPh)_2$ |
| **2** | SPh | **5** | $PO(OMe)_2$ |
| **3** | $SO_2Ph$ | **6** | OH |

Phthalide-3-phosphonates, **4** and **5**, were usually synthesized by the reaction of 3-hydroxyphthalides **6** with diphenyl or dimethyl phosphonates under thermal or base-catalyzed conditions reported by Yamaguchi and Okazaki[5] or Napolitano et al.[6] However, there remains a problem associated with accessibility of the starting 3-hydroxyphthalides **6** having substituents on the aromatic ring. We report here an efficient method for the synthesis of dimethyl phthalide-3-phosphonates **5** by the reaction of *N,N*-diethyl-2-formylbenzamides, which are easily obtained via a sequential directed ortho lithiation–formylation of *N,N*-diethylbenzamides,[2] with *tert*-butyldimethylsilyl dimethyl phosphite[9] followed by desilylation and cyclization using methanesulfonic acid under mild reaction conditions.

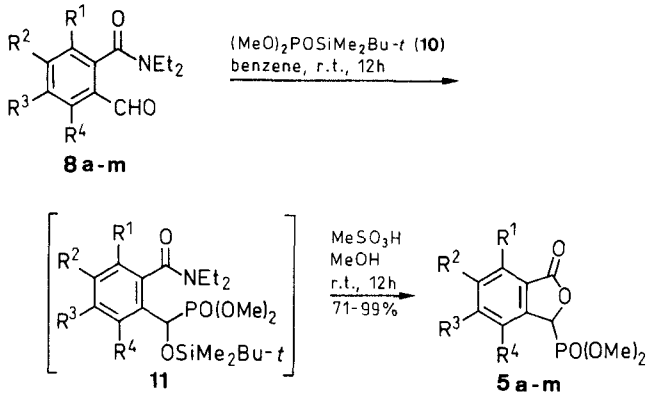



| 7,8 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | 7,8 | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|---|---|---|---|
| **a** | H | H | H | H | **g** | H | H | MeO | MeO |
| **b** | H | H | H | MeO | **h** | H | H | $OCH_2O$ | |
| **c** | MeO | H | H | MeO | **i** | H | MeO | MeO | MeO |
| **d** | MeO | H | H | H | **j** | MeO | H | MeO | MeO |
| **e** | H | H | MeO | H | **k** | $(CH{=}CH)_2$ | | H | H |
| **f** | MeO | MeO | H | H | | | | | |

**Scheme 1**

*N,N*-Diethyl aromatic amides **7a–k** were lithiated with 1.2 equivalents of *sec*-butyllithium in the presence of 1.2 equivalents of *N,N,N′,N′*-tetramethylethylenediamine

(TMEDA) at −78 °C and reacted with 2.0 equivalents of dimethylformamide (DMF) to give *N,N*-diethyl-2-formylbenzamides **8a–k** in 56–94% yield (Scheme 1). For the synthesis of 2-formyl-4,5-dimethoxybenzamide **8l**, a halogen–lithium exchange reaction was employed. 2-Bromo-*N,N*-diethyl-3,4-dimethoxybenzamide (**7l**) was treated with 1.2 equivalents of butyllithium at −105 °C for 40 minutes and quenched with 2.0 equivalents of DMF to afford **8l** in 60% yield. However, when this method was applied to the preparation of *N,N*-diethyl-2-formyl-4,5-methylenedioxybenzamide (**8m**) starting from 2-bromo-*N,N*-diethyl-4,5-methylenedioxybenzamide (**7m**), the desired **8m** was yielded as a minor product (16% yield) and the regioisomer **8h** was obtained as the major product (36% yield). Therefore, the directed lithiation strategy[2] using **7h** was employed. Lithiation of **7h** under standard conditions followed by treatment with chlorotrimethylsilane gave silylated compound **9**. Without purification, compound **9** was converted into **8m** by the sequential lithiation–formylation and then desilylation with tetrabutylammonium fluoride (TBAF) in 60% overall yield. Among the 2-formylbenzamides prepared in Scheme 1, **8a**,[10] **8b**,[11] **8c**,[12] **8d**,[11] and **8f**[11] were known compounds, but the others had not been characterized. The structures of new 2-formylbenzamides **8e**, **8g–m** were established by IR, UV, $^1$H NMR, MS data and elemental analyses. Physical properties and spectral data of **8e** and **8g–m** are listed in Table 1.




| 5, 8, 11 | R$^1$ | R$^2$ | R$^3$ | R$^4$ | 5, 8, 11 | R$^1$ | R$^2$ | R$^3$ | R$^4$ |
|---|---|---|---|---|---|---|---|---|---|
| **a** | H | H | H | H | **h** | H | H | $OCH_2O$ | |
| **b** | H | H | H | MeO | **i** | H | MeO | MeO | MeO |
| **c** | MeO | H | H | MeO | **j** | MeO | H | MeO | MeO |
| **d** | MeO | H | H | H | **k** | $(CH{=}CH)_2$ | | H | H |
| **e** | H | H | MeO | H | **l** | H | MeO | MeO | H |
| **f** | MeO | MeO | H | H | **m** | H | $OCH_2O$ | | H |
| **g** | H | H | MeO | MeO | | | | | |

**Scheme 2**

In 1978, Evans and co-workers prepared and demonstrated the utility of *tert*-butyldimethylsilyl dimethyl phosphite (**10**) during their study of the addition reactions of several tervalent phosphorus–silicon reagents with a range of carbonyl substrates.[9] The reagent **10** reacts smoothly with benzaldehyde to produce dimethyl α-(*tert*-butyldimethylsilyloxy)benzylphosphonate in 65% yield.[9] Reaction of 1.0 equivalent of *N,N*-diethyl-2-formylbenzamide (**8a**) with 2.0 equivalents of *tert*-butyldimethylsilyl dimethyl phosphite (**10**) in benzene at room temperature for 12 hours gave the adduct **11a** as an oily product which, without isolation, was used for the next step. Treatment of **11a** with 2.0 equivalents of methanesulfonic acid in methanol at room temperature for 12 hours afforded dimethyl phthalide-3-phosphonate (**5a**)[6] in almost quantitative yield. Under similar conditions, a variety of substituted dimethyl phthalide-3-phosphonates, **5b–m**, as shown in Scheme 2 were synthesized in a one-pot process in high yields from the corresponding formylbenzamides **8b–m**. In entries 6 and 7, the 2-formylbenzamides **8f** and **8g**, were allowed to react with **10** in refluxing tetrahydrofuran for 2 hours due to poor solubility and then treated with methanesulfonic acid to give **5f** and **5g** in 90% and 75% yield, respectively. Physical properties and spectral data for **5a–m** are listed in Table 2.

When we applied Yamaguchi's conditions[5] or Napolitano's procedure[6] for the synthesis of dimethyl phthalide-3-phosphonates **5** starting from *N,N*-diethyl-2-formylbenzamides **8a–c** and **8k**, the yields of the corresponding phthalides **5a–c** and **5k** were found to be variable and not satisfactory as shown in parenthesis in Table 2.

In conclusion, we have found that highly substituted dimethyl phthalide-3-phosphonates **5** were regioselectively synthesized by a two-step procedure which involved lithiation–formylation of *N,N*-diethylbenzamides **9** and reaction of *N,N*-diethyl-2-formylbenzamides **8** with *tert*-butyldimethylsilyldimethyl phosphite (**10**). Compared with previous procedures[5,6] for phthalide-3-phosphonates, our method has the advantages of greater generality, convenience, and high yields.

The IR spectra were measured in a KBr disk with a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% EtOH on a Hitachi 323 spectrophotometer. The $^1$H NMR spectra were obtained with a JEOL FX 90Q (90 MHz) spectrometers using $CDCl_3$ as a solvent and TMS as an internal reference. The MS and high-resolution MS (HRMS) were determined on a JEOL DX-303 mass spectrometer. Elemental anaylses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reaction were freshly distilled from sodium benzophenone ketyl before use. All metalation reactions were carried out in an argon atmosphere by using the septum cap techniques. Conventional column flash chromatography was carried out on a column of Kieselgel 60 (230–400 mesh).

***N,N*-Diethyl-2-formylbenzamides (8); General Procedure:**
A solution of *s*-BuLi (1.00 M in cyclohexane, 3.60 mmol) was injected into a stirred solution of *N,N*-diethylbenzamides **7** (3.00 mmol) in the presence of TMEDA (3.60 mmol) in THF (60 mL) at −78 °C (dry ice/acetone bath) under an Ar atmosphere. The mixture was stirred at −78 °C for 1 h, then a solution of DMF (6.00 mmol) in THF (10 mL) was injected into the lithiated solution at −78 °C. After 30 min, the cooling bath was removed and the solution was allowed to warm to r.t. and stirring was continued for an additional 2 h. The mixture was quenched with sat. aq $NH_4Cl$ solution, and evaporated under reduced pressure. The residue was extracted with $CH_2Cl_2$ and the organic layer was evaporated to give a residue, which was chromatographed using EtOAc as an eluent to give *N,N*-diethyl-2-formylbenzamides **8** (Scheme 2).

**Table 1.** Physical Properties and Spectral Data of *N,N*-Diethyl-2-formylbenzamides **8** Prepared

| Compound | Yield (%) | mp (°C)[a] (solvent) or bp (°C)/ mbar[a] | Molecular Formula[c] or Lit. bp (°C)/ mbar or mp (°C) | IR $\nu_{CO}$ ($cm^{-1}$) | UV (EtOH) $\lambda_{max}$ (nm) (log ε) | $^1H$ NMR ($CDCl_3$) δ, J (Hz) | MS m/z ($M^+$) |
|---|---|---|---|---|---|---|---|
| **8a** | 59 | 130/0.4 | oil[10] | 1700, 1630 | 208 (4.17), 232 (3.93), 245 (s) (3.91), 287 (3.37) | 1.03 (3H, t, J = 7.0), 1.33 (3H, t, J = 7.0), 3.13 (2H, q, J = 7.0), 3.59 (2H, t, J = 7.0), 7.26–8.00 (4H, m), 10.02 (1H, s) | 205 |
| **8b** | 60 | oil | 140–145/0.1[11] | 1690, 1630 | 213 (4.33), 258 (3.65), 322 (3.61) | 0.96 (3H, t, J = 7.2), 1.26 (3H, t, J = 7.2), 3.03 (2H, q, J = 7.2), 3.53 (2H, q, J = 7.2), 3.86 (3H, s), 6.96–7.66 (3H, m), 10.48 (1H, s) | 235 |
| **8c** | 80 | 100–102 ($Et_2O$) | 97–99[12] | 1690, 1630 | 207 (4.29), 223 (s) (4.20), 260 (3.64), 360 (3.67) | 1.00 (3H, t, J = 7.1), 1.30 (3H, t, J = 7.1), 3.07 (2H, q, J = 7.1), 3.50 (2H, q, J = 7.1), 3.76 (3H, s), 3.86 (3H, s), 6.89 (1H, d, J = 8.0), 7.10 (1H, d, J = 8.0), 10.43 (1H, s) | 265 |
| **8d** | 87 | oil | 125–130/0.08[11] | 1700, 1630 | 210 (4.29), 253 (3.73), 315 (3.46) | 0.98 (3H, t, J = 7.2), 1.27 (3H, t, J = 7.2), 3.09 (2H, q, J = 7.2), 3.58 (2H, q, J = 7.2), 3.84 (3H, s), 7.06–7.47 (3H, m), 9.94 (1H, s) | 235 |
| **8e** | 68 | 160/0.8 | $C_{13}H_{17}NO_3$ (235.3) | 1700, 1630 | 203 (4.21), 223 (s) (4.37), 250 (s) (3.80), 315 (3.36) | 1.04 (3H, t, J = 7.0), 1.29 (3H, t, J = 7.0), 3.16 (2H, q, J = 7.0), 3.60 (2H, q, J = 7.0), 3.86 (3H, s), 7.08–7.44 (3H, m), 10.02 (1H, s) | 235 |
| **8f** | 60 | oil | 170/0.35[11] | 1690, 160 | 203 (4.27), 227 (s) (4.08), 276 (4.01), 298 (3.86) | 1.03 (3H, t, J = 7.1), 1.30 (3H, t, J = 7.1), 3.10 (2H, q, J = 7.1), 3.59 (2H, q, J = 7.1), 3.83 (3H, s), 3.92 (3H, s), 6.96 (1H, d, J = 8.0), 7.56 (1H, d, J = 8.0), 9.69 (1H, s) | 265 |
| **8g** | 70 | 155/0.2 | $C_{14}H_{19}NO_4$ (265.3) | 1690, 1630 | 206 (s) (3.92), 225 (3.95), 260 (3.41), 325 (3.07) | 1.00 (3H, t, J = 7.2), 1.30 (3H, t, J = 7.2), 3.03 (2H, q, J = 7.2), 3.50 (2H, q, J = 7.2), 3.86 (3H, s), 3.92 (3H, s), 6.79 (1H, d, J = 9.0), 7.07 (1H, d, J = 9.0), 10.23 (1H, s) | 265 |
| **8h** | 70 | 88–90 ($Et_2O$) | $C_{13}H_{15}NO_4$ (249.3) | 1690, 1620 | 204 (4.31), 232 (4.23), 257 (s) (3.81), 288 (s) (3.09), 345 (3.59) | 1.05 (3H, t, J = 7.0), 1.29 (3H, t, J = 7.0), 3.16 (2H, q, J = 7.0), 3.56 (2H, q, J = 7.0), 6.16 (2H, s), 6.76 (1H, d, J = 7.9), 7.00 (1H, d, J = 7.9), 10.09 (1H, s) | 249 |
| **8i** | 56 | 69–70 ($Et_2O$) | $C_{15}H_{21}NO_5$ (295.3) | 1680, 1630 | 237 (4.34), 286 (4.05) | 1.00 (3H, t, J = 7.0), 1.33 (3H, t, J = 7.0), 3.07 (2H, q, J = 7.0), 3.56 (2H, q, J = 7.0), 3.89 (3H, s), 3.92 (3H, s), 4.03 (3H, s), 6.56 (1H, s), 10.55 (1H, s) | 295 |
| **8j** | 60 | 89–90 ($Et_2O$) | $C_{15}H_{21}NO_5$ (295.3) | 1690, 1630 | 202 (4.37), 222 (s) (4.31), 265 (3.71), 320 (3.65) | 0.99 (3H, t, J = 7.3), 1.30 (3H, t, J = 7.3), 3.07 (2H, q, J = 7.3), 3.59 (2H, q, J = 7.3), 3.82 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 6.74 (1H, s), 10.35 (1H, s) | 295 |
| **8k** | 94 | 64–65 ($Et_2O$) | $C_{16}H_{17}NO_2$ (255.3) | 1690, 1620 | 227 (4.29), 252 (4.66), 290 (3.83), 300 (3.83) | 0.92 (3H, t, J = 7.2), 1.39 (3H, t, J = 7.2), 3.03 (2H, q, J = 7.2), 3.75 (2H, q, J = 7.2), 7.55–8.00 (6H, m), 10.24 (1H, s) | 255 |
| **8l** | 60 | 86–87 ($Et_2O$) | $C_{14}H_{19}NO_4$ (265.3) | 1690, 1630 | 237 (4.36), 282 (4.01), 314 (3.85) | 1.07 (3H, t, J = 7.8), 1.31 (3H, t, J = 7.8), 3.17 (2H, q, J = 7.8), 3.63 (2H, q, J = 7.8), 3.96 (6H, s), 6.80 (1H, s), 7.45 (1H, s) 9.93 (1H, s) | 265 |
| **8m** | 60 | 175/0.15 | $C_{13}H_{15}NO_4$ (249.3) | 1695, 1630 | 235 (4.12), 266 (s) (3.61), 322 (3.41) | 1.08 (3H, t, J = 7.3), 1.31 (3H, t, J = 7.3), 3.16 (2H, q, J = 7.3), 3.60 (2H, q, J = 7.3), 6.19 (2H, s), 6.76 (1H, s), 7.36 (1H, s), 9.98 (1H, s) | 249 |

[a] Uncorrected, measured with a Yanagimoto micromelting point apparatus.
[b] Kugelrohr distillation with a Shibata GTO-250 R apparatus.
[c] For new compounds, satisfactory microanalyses obtained: C ±0.34, H ±0.19, N ±0.17.

Compounds **8l,m** were prepared by following procedures:

A solution of BuLi (1.20 M in hexane, 3.00 mL, 3.60 mmol) was injected into a stirred solution of 2-bromo-*N,N*-diethyl-4,5-dimethoxybenzamide (**7l**; 0.95 g, 3.00 mmol) and TMEDA (0.42 g, 3.60 mmol) in THF (60 mL) at −105 °C (liquid $N_2$/EtOH bath) under an Ar atmosphere. The mixture was stirred at −105 °C for 40 min, then a solution of DMF (0.44 g, 6.00 mmol) in THF (10 mL) was injected into the lithiated solution at −105 °C. The cooling bath was removed and stirring was continued for an additional 1 h. Standard work-up and chromatographic purification gave *N,N*-diethyl-2-formyl-4,5-dimethoxybenzamide (**8l**). Further purification by recrystallization from $Et_2O$ gave pure **8l** (0.48 g, 60%), mp 86–87 °C.

When the above procedure was applied for the preparation of *N,N*-diethyl-2-formyl-4,5-methylenedioxybenzamide (**8m**) starting from 2-bromo-*N,N*-diethyl-4,5-methylenedioxybenzamide (**7m**; 0.90 g, 3.00 mmol), **8m** (0.12 g, 16%) and *N,N*-diethyl-2-formyl-3,4-methylenedioxybenzamide (**8h**: 0.27 g, 36%) were obtained after silica gel column chromatographic separation.

Lithiation of *N,N*-diethyl-3,4-methylenedioxybenzamide (**7h**; 0.66 g, 3.00 mmol) in THF (60 mL) under the standard conditions (*s*-BuLi in cyclohexane solution: 3.60 mL, 3.60 mmol, TMEDA: 0.42 g, 3.60 mmol, −78 °C for 1 h) followed by addition of $ClSiMe_3$ (0.40 g, 3.60 mmol) at −78 °C and standard workup gave **9** as an oil. Without purification, compound **9** was again lithiated under the

**Table 2.** Physical Properties and Spectral Data of Dimethyl Phthalide-3-phosphonates **5** Prepared

| Compound | Yield (%) | mp (°C)[a] (solvent) | Molecular Formula[c] or Lit. mp (°C) | IR $\nu_{CO}$ ($cm^{-1}$) | UV (EtOH) $\lambda_{nm}$ (nm) (log ε) | $^1H$ NMR ($CDCl_3$) δ, J (Hz) | MS m/z ($M^+$) |
|---|---|---|---|---|---|---|---|
| **5a** | 99 (39)[c] | 95–96 (EtOAc) | 97–99[6] | 1775 | 229 (4.01), 234 (s) (3.97), 276 (3.33), 283 (3.33) | 3.65 (3H, d, $J$ = 10.8), 3.93 (3H, d, $J$ = 10.8), 5.84 (1H, d, $J$ = 11.4), 7.50–8.00 (4H, m) | 242 |
| **5b** | 93 (87)[c] | 165 (MeOH/ benzene) | $C_{11}H_{13}O_6P$ (272.2) | 1785 | 237 (s) (3.59), 298 (3.80) | 3.75 (3H, d, $J$ = 10.2), 3.86 (3H, d, $J$ = 10.2), 3.95 (3H, s), 5.73 (1H, d, $J$ = 9.6), 7.10–7.55 (3H, m) | 272 |
| **5c** | 99 (47)[c] | 194 (MeOH/ EtOAc) | $C_{12}H_{15}O_7P$ (302.2) | 1785 | 221 (4.44), 241 (3.88), 329 (3.79) | 3.76 (3H, d, $J$ = 9.5), 3.88 (3H, d, $J$ = 9.5), 3.91 (3H, s), 3.95 (3H, s), 5.68 (1H, d, $J$ = 11.1), 6.92 (1H, d, $J$ = 9.0), 7.14 (1H, d, $J$ = 9.0) | 302 |
| **5d** | 71 | 140–141 (EtOAc) | $C_{11}H_{13}O_6P$ (272.2) | 1788 | 230 (s) (4.29), 237 (4.35), 243 (s) (4.31), 302 (4.24) | 3.54 (3H, d, $J$ = 10.2), 3.81 (3H, d, $J$ = 10.2), 3.89 (3H, s), 5.57 (1H, d, $J$ = 10.8), 6.87–7.73 (3H, m) | 272 |
| **5e** | 74 | 77–78 (EtOAc) | $C_{11}H_{13}O_6P$ (272.2) | 1760 | 210 (4.29), 254 (4.18), 273 (s) (3.78), 284 (3.49) | 3.64 (3H, d, $J$ = 10.6), 3.94 (3H, d, $J$ = 10.6), 5.67 (1H, d, $J$ = 11.0), 7.11 (1H, d, $J$ = 8.4), 7.16 (1H, s), 7.82 (1H, d, $J$ = 8.4) | 272 |
| **5f** | 90[d] | 68–69 (EtOAc) | 84–87[6] | 1770 | 213 (4.18), 238 (s) (3.60), 310 (3.33) | 3.63 (3H, d, $J$ = 10.5), 3.92 (3H, d, $J$ = 10.5), 5.59 (1H, d, $J$ = 9.7), 7.29–7.44 (2H, m) | 302 |
| **5g** | 75[d] | 112–114 (EtOAc/ $Et_2O$) | $C_{12}H_{15}O_7P$ (302.2) | 1770 | 211 (s) (4.38), 220 (4.40), 261 (4.10), 290 (s) (3.37) | 3.78 (3H, d, $J$ = 12.5), 3.93 (3H, d, $J$ = 12.5), 4.00 (3H, s), 4.02 (3H, s), 5.76 (1H, d, $J$ = 9.7), 7.13 (1H, d, $J$ = 8.4), 7.65 (1H, d, $J$ = 8.4) | 302 |
| **5h** | 99 | 152–153 (EtOAc) | $C_{11}H_{11}O_7P$ (286.2) | 1760 | 208 (4.29), 226 (4.40), 271 (3.81), 297 (3.79) | 3.78 (3H, d, $J$ = 10.6), 3.91 (3H, d, $J$ = 10.6), 5.70 (1H, d, $J$ = 9.4), 6.20 (2H, d, $J$ = 8.8), 7.04 (1H, d, $J$ = 7.9), 7.54 (1H, d, $J$ = 7.9) | 286 |
| **5i** | 92 | 85–86 (EtOAc/ $Et_2O$) | $C_{13}H_{17}O_8P$ (332.2) | 1788 | 221 (4.61), 263 (4.19), 296 (s) (3.86), 304 (3.89) | 3.75 (3H, d, $J$ = 11.0), 3.90 (3H, d, $J$ = 11.0), 3.93 (3H, s), 3.94 (3H, s), 4.05 (3H, s), 5.70 (1H, d, $J$ = 9.0), 7.16 (1H, s) | 332 |
| **5j** | 99 | 126–127 ($CH_2Cl_2$/ EtOAc) | $C_{13}H_{17}O_8P$ (332.2) | 1760 | 212 (4.34), 225 (4.44), 257 (4.04), 306 (3.91) | 3.78 (3H, d, $J$ = 9.4), 3.90 (3H, d, $J$ = 9.4), 3.91 (3H, s), 3.98 (6H, s), 5.67 (1H, d, $J$ = 9.7), 6.52 (1H, s) | 332 |
| **5k** | 80 (30)[c] | 149–150 (EtOAc) | $C_{14}H_{13}O_5P$ (292.2) | 1785 | 214 (s) (4.55), 225 (s) (4.51), 239 (4.49), 243 (s) (4.46), 301 (4.10), 311 (s) (3.97), 324 (3.80) | 3.60 (3H, d, $J$ = 10.6), 3.96 (3H, d, $J$ = 10.6), 5.79 (1H, d, $J$ = 12.3), 7.57–8.23 (5H, m), 8.99 (1H, d, $J$ = 6.2) | 292 |
| **5l** | 82 | 127–130 (EtOAc) | $C_{12}H_{15}O_7P$ (302.2) | 1770 | 226 (4.50), 261 (3.98), 296 (3.86), 300 (s) (3.84) | 3.60 (3H, d, $J$ = 10.1), 3.94 (3H, d, $J$ = 10.1), 4.00 (6H, s), 5.62 (1H, d, $J$ = 10.1), 7.16 (1H, s), 7.30 (1H, s) | 302 |
| **5m** | 79 | 116–117 (EtOAc) | $C_{11}H_{11}O_7P$ (286.2) | 1770 | 226 (4.44), 262 (3.69), 303 (3.85), 308 (s) (3.82) | 3.67 (3H, d, $J$ = 10.6), 3.92 (3H, d, $J$ = 10.6), 5.57 (1H, d, $J$ = 10.8), 6.15 (2H, s), 7.09 (1H, s), 7.22 (1H, s) | 286 |

[a] Uncorrected, measured with a Yanagimoto micromelting point apparatus.
[b] Satisfactory microanalyses obtained: C ±0.22, H ±0.32.
[c] Direct synthesis using $HPO(OMe)_2$.
[d] Refluxing THF for 2 h, then treatment with $MeSO_3H$.

conditions described above and then a solution of DMF (0.44 g, 6.00 mmol) in THF (10 mL) was injected into the lithiated solution at −78 °C. The solution was allowed to warm to r.t. and stirring was continued for an additional 1 h. Standard work-up gave an oily product which, without purification, was dissolved in $Et_2O$ (30 mL). A solution of TBAF (1.00 M in THF: 3.00 mL, 3.00 mmol) was added to the above solution at r.t. with stirring. The mixture was stirred at r.t. for 1 h, then evaporated to give a residue which was chromatographed with EtOAc as an eluent to afford **8m** (0.45 g, 60%), an oil.

Physical properties and spectral data of *N,N*-diethyl-2-formylbenzamides **8a–m** thus prepared are summarized in Table 1.

**Dimethyl Phthalide-3-phosphonates 5a–m; General Procedure:**
A solution of *tert*-butyldimethylsilyl dimethyl phosphite[9] (**10**; 4.00 mmol) and *N,N*-diethyl-2-formylbenzamide **8** (2.00 mmol) in benzene (10 mL) was stirred for 12 h at r.t. After removal of solvent under reduced pressure, the residual phosphonate **11** was dissolved in MeOH (10 mL). A solution of $MeSO_3H$ (4.00 mmol) in MeOH (5 mL) was added to the solution of **11** at r.t. with stirring. The mixture was stirred at r.t. for 12 h and evaporated. The residue was extracted with $CH_2Cl_2$ and the organic layer was washed sequentially with 5% aq $NaHCO_3$ and then with sat. aq NaCl, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography using EtOAc as an eluent to afford dimethyl phthalide-3-phosphonates **5** (Table 2).

Physical properties and spectral data of **5a–m** thus synthesized are summarized in Table 3.

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