An Improved Synthesis of Cyclopropanes from Stabilized Phosphonates and 1,2-Dioxines

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Abstract: Addition of stabilized Horner−Wadsworth−Emmons (HWE) phosphonates to substituted 1,2-dioxines leads to diastereomerically pure di- and trisubstituted cyclopropanes in high yields and represents a viable alternative to ylides in the cyclopropanation reaction involving 1,2-dioxines. While yields are comparable, reaction times with these stabilized phosphonates were accelerated and the diastereoselectivity for this cyclopropanation reaction was significantly greater than for the previously reported examples employing ylides.

The cyclopropyl moiety plays an important role in many natural and nonnatural products.[1] While many methods exist for the synthesis of diastereo- and enantiopure disubstituted cyclopropanes, there are limited means for the synthesis of trisubstituted cyclopropanes in high de and/or ee.[2,3] The use of stabilized ylides and 1,2-dioxines in generating diastereomerically pure trisubstituted cyclopropanes has been previously described by our group (Figure 1).[4,5] The reaction has been shown to proceed by the reactive *cis*-γ-hydroxy enone **2** which can arise via base-induced rearrangement or cobalt-assisted radical rearrangement of 1,2-dioxines, **1**. Subsequent syn 1,4-Michael addition of stabilized ylides (nonbulky, R^1 = Me, Et, Bn or bulky, R^1 = 1-adamantyl, Bu^t) to the enone then leads, via the oxaphospholane intermediate **3**, to either of the cyclopropyl isomers, **4** or **5**, depending on the steric nature of the ylide, i.e., nonbulky (pathway A)[4] or bulky (pathway B).[5] Additionally, the pathway that the reaction takes can be influenced by the introduction of lithium bromide which promotes reaction pathway B even in the presence of nonbulky ylides.[5]

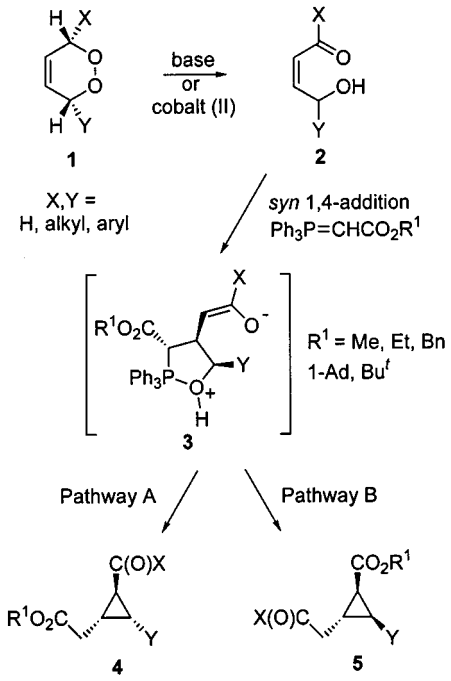

Figure 1. Formation of cyclopropanes **4** and/or **5** from 1,2-dioxines and stabilized phosphorus ylides.[4,5]

The base-induced rearrangement of the 1,2-dioxine to the *cis*-γ-hydroxy enone and the subsequent 1,4-addition of the stabilized ylide depends on the basicity and nucleophilicity of the ylide used. While the majority of the cyclopropanation reactions are facile, reaction times of up to 6 days or more have been reported.[4] This is primarily due to the fact that while ylide basicity is sufficient to induce ring-opening of the 1,2-dioxine, subsequent 1,4-Michael addition can be slow due to insufficient ylide nucleophilicity.[5,6] This paper describes the use of stabilized Horner−Wadsworth−Emmons (HWE) phosphonates for the cyclopropanation process, which are known to be more nucleophilic than their corresponding ylide counterparts.[7,8] Also reported are the use of cyano and Weinreb type phosphonates in the cyclopropanation process which allows a greater diversity of functional groups on the cyclopropane.[9] It must be noted that HWE phosphonates have been previously utilized for the synthesis of cyclopropanes from their addition to epoxides. However, one drawback is that the synthesis of

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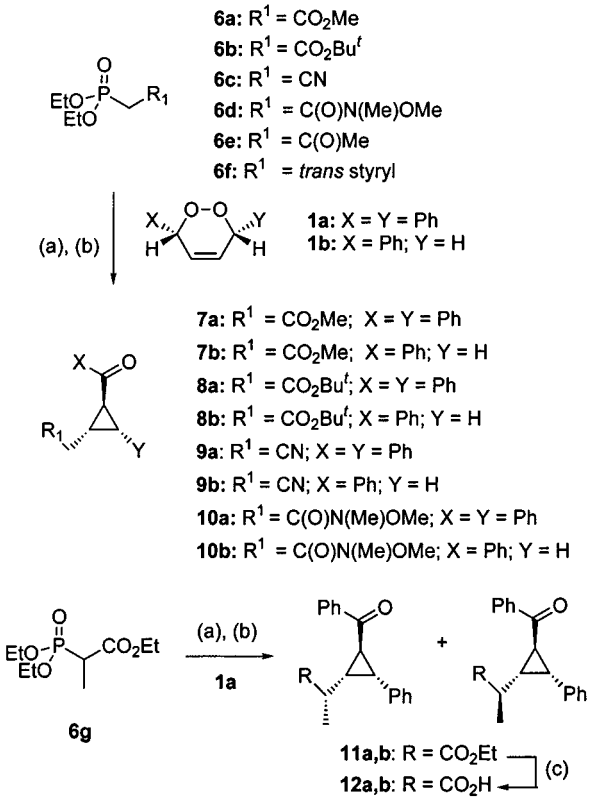
Scheme 1[a]



[a] (a) MeLi, THF, 0 °C; (b) 1,2-dioxine, rt, 3 h; (c) MeOH, NaOH.

enantiopure cyclopropanes relies on the synthesis of the corresponding enantiopure epoxides.[10]

HWE phosphonates and 1,2-dioxines chosen for this study are depicted in Scheme 1 with results summarized in Table 1. While dioxines **1a** and **1b** have been utilized in this study, these cyclopropanations would be equally applicable to a range of alkyl−alkyl and alkyl−aryl dioxines.[4,5]

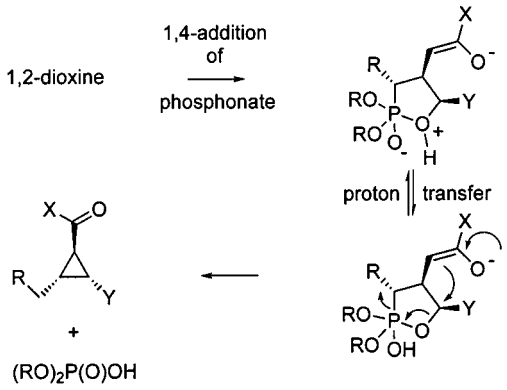
The base chosen for deprotonation of the phosphonates was methyllithium since it proved to be clean and reliable. Phosphonates **6a**−**d** gave moderate to high yields of the expected cyclopropanes, with both the symmetrical and nonsymmetrical 1,2-dioxines, **1a** and **1b**, respectively. Addition of LiBr did not affect the diastereoselectivity of the reaction; however, it has been noted that THF strongly favors pathway A. Reaction of **1a** with **6a** in benzene in the presence (entry 4) and absence (entry 3) of LiBr afforded **7a** as the sole product. In addition, the bulky *tert*-butyl ester phosphonate **6b** gave cyclopropanes **8a** and **8b** both derived from reaction pathway A. These results suggest that oxaphospholane intermediate **3** described in Figure 1 collapses via pathway A exclusively when HWE phosphonates are employed. Cyclopropanes which derive from pathway B (Figure 1, structure **5**) result from an intramolecular quenching of the keto-enolate, **3**.[5] Therefore, a possible explanation for the regioselectivity of the reaction when HWE phosphonates are employed is that this quenching

Table 1. Reaction of 1,2-Dioxines 1a,b with Various Stabilized Phosphonates 6a−g[a]

entry	phosphonate	1,2-dioxine	product	yield (%)[b]
1	**6a**	**1a**	**7a**	81
2[c]				(60)
3[d]				(61)
4[e]				(62)
5		**1b**	**7b**	80
6	**6b**	**1a**	**8a**	75
7		**1b**	**8b**	70
8	**6c**	**1a**	**9a**	53
9		**1b**	**9b**	51
10	**6d**	**1a**	**10a**	91
11		**1b**	**10b**	64
12	**6e**	**1a**	-	-
13		**1b**	-	-
14	**6f**	**1a**	-	-
15		**1b**	-	-
16[f]	**6g**	**1a**	**11a** and **11b**	30
17[g]				(25)

[a] Reaction carried out as in Experimental Section. [b] Yields in parentheses were determined by ^{1}H NMR. [c] One equivalent of LiBr present. [d] Reaction carried out in benzene. [e] Reaction carried out in benzene in the presence of 1 equiv of LiBr. [f] Cyclopropanes isolated as a 1:1 mixture of diastereomers, which were separated by PTLC and fully characterized via their acid derivatives **12a** and **12b**. [g] KHMDS used as base in place of MeLi.

Scheme 2



mechanism does not occur. This could conceivably be from a competitive proton transfer (Scheme 2).

The cyano phosphonate **6c** yielded the corresponding cyano cyclopropanes **9a** and **9b** in modest yield. Of particular interest was the moderate to high yields of the Weinreb cyclopropanes **10a** and **10b**, derived from phosphonate **6d**, and to our knowledge the first reported direct generation of Weinreb protected cyclopropanes without functional group manipulation. As previously reported with the methyl-keto ylide, the methyl-keto phosphonate **6e** gave no cyclopropane with either **1a** or **1b**, as did phosphonate **6f,** due to a competitive Kornblum−De La Mare rearrangement to afford 1,4-diketone.[4,11] α-Methyl-substituted phosphonate **6g** gave moderate yields of the desired cyclopropanes as a mixture of diastereomers **11a** and **11b** (entry 16). In an attempt to increase the yield of cyclopropanes **11a** and **11b**, a different base, KHMDS, was tried, but it proved unsuccessful. Cyclopropanation reactions involving phosphonates **6a**−**d** were significantly faster (3 h) than for the previously reported ylides. This indicates that the increased nucleophilicity of these stabilized phosphonates

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facilitates their 1,4-addition to the *cis*-γ-hydroxy enones **2**. One precautionary point is that if the cyclopropanation reaction is left longer than this period or the reaction is quenched with methanol instead of an ammonium chloride solution, significant amounts of rearranged products can be detected.[12] As expected, since phosphonate **6f** has a low degree of anion stabilization as compared to phosphonates **6a**−**e** and **6g**, it gave no 1,4-addition to the *cis*-γ-hydroxy enone **2** and subsequent formation of 1,4-diketone. Additionally, phosphonate **6g** also gave significant amounts of 1,4-diketone, implying that the α-methyl substitution reduces the phosphonates nucleophilicity and subsequent ability to perform the 1,4-addition to the enone **2**.

In summary, addition of stabilized Horner−Wadsworth−Emmons (HWE) phosphonates to substituted 1,2-dioxines leads to diastereomerically pure di- and trisubstituted cyclopropanes in high yields and represents a viable alternative to ylides in the cyclopropanation reaction involving 1,2-dioxines. While yields are comparable, reaction times with these stabilized phosphonates were accelerated, and the diastereoselectivity for this cyclopropanation reaction was significantly greater than for the previously reported examples employing ylides.

Experimental Section

General. Solvents were dried by appropriate methods wherever needed. All organic extracts were dried over anhydrous magnesium sulfate. Thin-layer chromatography (TLC) used aluminum sheets silica gel 60 F_{254} (40 × 80 mm) from Merck. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. Infrared spectra were recorded as either Nujol mulls or in the neat form as denoted. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on either a 300 MHz or 600 MHz instrument, using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. HRMS were performed by the Organic Mass Spectrometry Facility, Central Science Laboratory, University of Tasmania. Microanalyses were performed at the University of Otago.

General Method. To solution of the phosphonate (1.2 equiv) in dry THF (10 mL) at 0 °C under a N_2 atmosphere was added a solution of MeLi (1.2 equiv) dropwise over 5 min. The reaction was stirred for a further 30 min, the 1,2-dioxine (1 equiv) was added, and the reaction was allowed to warm to room temperature over a 3 h period (with TLC monitoring). The reaction was quenched with a solution of sat. NH_4Cl. The aqueous layer was then extracted with dichloromethane, the resultant organic extracts were dried and filtered, and the solvent was removed in vacuo. The pure cyclopropanes were then obtained by column chromatography or recrystallization. Cyclopropanes **7a**, **7b**, **8a**, **8b**, and **12a** have been previously reported.[4,5] This method yielded the following new cyclopropanes.

***trans*-(±)-(2-Benzoyl-3-phenylcyclopropyl)methyl Cyanide, 9a.** Straw-colored oil (R_f 0.35, 80:20, hexane:ethyl acetate); IR (oil) 3085, 3060, 3029, 2250, 1668, 1450, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.18 (m, 1H), 2.29 (m, 2H), 3.06 (dd, J = 4.8, 5.4 Hz, 1H), 3.09 (dd, J = 4.8, 9.0 Hz, 1H), 7.17 (m, 3H), 7.31 (m, 2H), 7.47 (m, 2H), 7.57 (m, 1H), 8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.4, 25.4, 29.0, 33.9, 118.1, 127.7, 128.2, 128.8, 128.9, 129.0, 133.4, 134.2, 137.3, 197.2; MS *m*/*z* (%) 261 (M^+, 10), 221 (38), 115 (28), 105 (100), 77 (68), 51 (20); HRMS calcd for $C_{18}H_{15}NO$: 261.1153; found 261.1114.

***trans*-(±)-(2-Benzoylcyclopropyl)methyl Cyanide, 9b.** Colorless oil (R_f 0.33, 80:20, hexane:ethyl acetate); IR (oil) 3060, 2213, 1685, 1595, 1421 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.92 (ddd, J = 4.2, 6.0, 10.2 Hz, 1H), 1.48 (m, 1H), 1.81 (m, 1H), 2.28 (dd, J = 7.8, 15.6 Hz, 1H), 2.48 (dd, J = 6.6, 15.6 Hz, 1H), 2.59 (m, 1H), 7.39 (m, 2H), 7.50 (m, 1H), 7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.6, 21.4, 24.4, 37.9, 51.8, 128.0, 128.5, 133.2, 137.8, 199.1; MS *m*/*z* (%) 185 (M^+, 10), 186 (20), 141 (30), 128 (20), 115 (45), 105 (100), 77 (30); HRMS calcd for $C_{12}H_{11}NO$: 185.0841; found 185.0839.

***trans*-(±)-*N*-Methoxy-*N*-methyl-2-(2-benzoyl-3-phenylcyclopropyl)acetamide, 10a.** Yellow oil (R_f 0.35, 70:30, hexane:ethyl acetate); IR (oil) 3060, 3027, 2967, 2937, 1668, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.15 (dd, J = 7.6, 16.0 Hz, 1H), 2.29 (m, 1H), 2.44 (dd, J = 6.6, 15.6 Hz, 1H), 3.03 (s, 3H), 3.09 (m, 2H), 3.38 (s, 3H), 7.15−7.26 (m, 5H), 7.43 (m, 2H), 7.50 (m, 1H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.7, 29.3, 30.7, 33.5, 36.0, 61.1, 126.8, 128.2, 128.4, 128.6, 129.0, 132.8, 138.0, 198.7, 203.9; MS *m*/*z* (%) 323.5 (M^+, 10), 292 (15), 262 (15), 233 (12), 220 (16), 129 (20), 105 (100), 77 (51). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.99; H, 6.49; N, 4.40.

***trans*-(±)-*N*-Methoxy-*N*-methyl-2-(2-benzoylcyclopropyl)acetamide, 10b.** Yellow oil (R_f 0.37, 70:30, hexane:ethyl acetate); IR (oil) 3057, 3002, 2972, 2939, 1740, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.95 (ddd, J = 3.6, 6.6, 10.2 Hz, 1H), 1.50 (m, 1H), 1.83 (m, 1H), 2.39 (dd, J = 7.2, 15.0 Hz, 1H), 2.57 (m, 1H), 2.62 (dd, J = 6.0, 15.0 Hz, 1H), 3.11 (s, 3H), 3.63 (s, 3H), 7.40 (m, 2H), 7.48 (m, 1H), 7.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.1, 21.8, 24.4, 30.9, 36.1, 61.3, 128.1, 128,5, 132.7, 138.0, 199.5, 206, 9; MS *m*/*z* (%) 248 (M^+, 30), 216 (17), 187 (26), 159 (20), 105 (100), 77 (19). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.98; N, 5.72.

***trans*-(±)-(2*R*)-2-(2-Benzoyl-3-phenylcyclopropyl)propanoic Acid, 12b.** White crystalline solid, mp 174.5−176 °C; IR 3060, 3000, 2975, 1725, 1670 cm^{-1}; IR (Nujol) 3055, 3000, 2975, 1690, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26 (d, J = 7.2 Hz, 3H), 1.97 (dt, J = 7.2, 10.2 Hz, 1H), 2.28 (ddd, J = 4.8, 9.6, 10.2 Hz, 1H), 2,97 (dd, J = 4.8, 5.4 Hz, 1H), 3.08 (dd, J = 5.4, 9.6 Hz, 1H), 7.17−7.26 (m, 5H), 7.44−7.56 (m, 3H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.9, 28.3, 34.3, 35.0, 37.8, 127.0, 128.1, 128.4, 128.8, 128.9, 133.1, 135.8, 137.6, 198.2, 204.9; MS *m*/*z* (%) 294 (M^+, 28), 276 (30), 249 (15), 221 (90), 105 (100), 77 (28). HRMS calcd for $C_{19}H_{18}O_3$: 294.1255; found 294.1255. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53. H, 6.16. Found: C, 76.88. H, 6.27.

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