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AN EFFICIENT METHOD FOR THE PREPARATION OF ALKYLIDENECYCLOPROPANES

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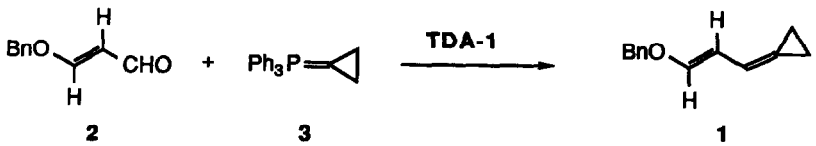
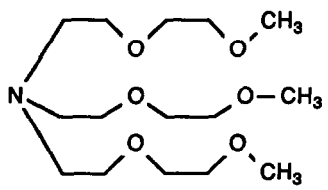
Abstract: *Yields obtained from Wittig reactions with cyclopropylidenetriphenylphosphorane are greatly improved by addition of the phase-transfer catalyst, TDA-1.*

During the course of a synthesis currently underway we needed to prepare the cyclopropylidenebenzyloxydiene **1**. Several methods of preparing alkylidenecyclopropanes have been reported,[1] and the area has seen a substantial amount of recent activity aimed at providing improved synthetic procedures. Unfortunately, the reported methods appear to suffer disadvantages, such as difficulty in obtaining the starting materials or low overall yield.

Clearly the most direct synthesis of **1** would involve the Wittig reaction between cyclopropylidenetriphenylphosphorane (**3**)[2] and (E)-3-benzyloxyacrolein (**2**).[3] Although low yields are often associated with using **3**, we believed that the brevity of the diene synthesis would compensate for a modest yield in the Wittig reaction, and we therefore undertook a brief study of the process.



2 **3** **1**



TDA-1

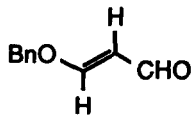
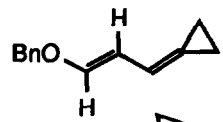
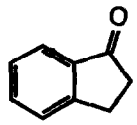
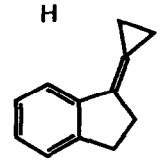
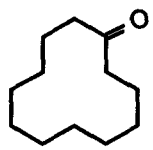
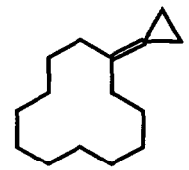
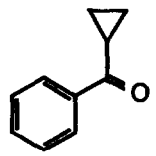
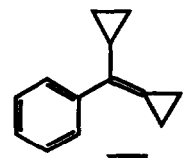
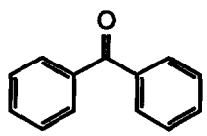
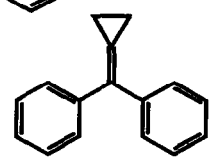
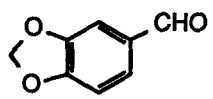
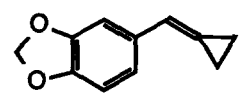
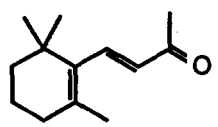
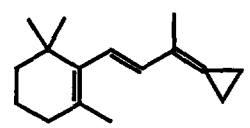
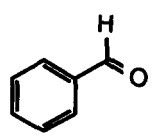
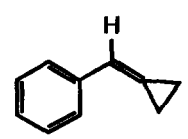
Initial attempts to carry out the Wittig reaction between **2** and **3** were uniformly unsuccessful. Standard methods led either to the recovery of unreacted **2** or to its complete decomposition. When conditions using NaH in dimethylformamide (DMF) along with a catalytic amount of 18-crown-6 were employed, the diene was isolated in yields ranging between 13% and 17%,[4] but no diene was seen when the crown ether was omitted. Furthermore, the reaction between **2** and **3** using 18-crown-6 in NaH/THF also failed to deliver the diene. We reasoned that the inability to achieve acceptable yields using phosphorane **3** might be due in part to its low solubility in the reaction medium. It therefore seemed necessary to find a different phase-transfer catalyst, ideally one that could be used in normal organic solvents rather than in DMF. In so doing, we could avoid the extractive work-up that could destroy the sensitive alkylidenecyclopropane products.

We were attracted to tris[2-(2-methoxyethoxy)ethyl]amine, TDA-1, because of its low cost, its low toxicity, and its compatibility with a range of solvents.[5] In practice, the reaction between **2** and **3** using NaH/THF and 10 mol % TDA-1 resulted in an 83% yield of diene **1** as the sole product. Omission of TDA-1 led to no reaction between **2** and **3**.[6] To our knowledge this represents the first use of TDA-1 as a catalyst in the Wittig reaction. Given the remarkable success of this reaction in yielding our desired diene, we were not surprised to find that this new use of TDA-1 has more general applications.

Results using TDA-1 as a catalyst in the Wittig reaction between **3** and a variety of carbonyl compounds are shown in the table. Isolated yields are good in all cases as shown by the following representative procedure. A solution of piperonal (530 mg, 3.53 mmol) and TDA-1 (114 mg, 10 mol %) in 5 mL THF was added to a stirring suspension of NaH (220 mg, 4.59 mmol, 50% oil dispersion prewashed with hexane) and cyclopropyltriphenylphosphonium bromide (1.76 g, 4.59 mmol) in 15 mL THF at room temperature. The resulting suspension was heated to 62°C and monitored by TLC. When there was no piperonal remaining, the orange reaction mixture was cooled, diluted with pentane (100mL), and passed through a short pad of silica gel. Evaporation of the solvent yielded pure piperonylidenecyclopropane (580 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): 7.12 (s,1H), 6.90 (d, 1H, 7.9 Hz), 6.75 (d, 1H, 7.9 Hz), 6.64 (bs, 1H), 5.93 (s, 2H), 1.39-1.11 (m, 4H); IR (neat): 2985, 2900,1490, 1255 cm^{-1}; ^{13}C NMR (100MHz, $CDCl_3$): 147.9, 146.5, 132.9, 122.2, 120.9, 117.9, 108.2, 106.2, 100.9, 4.1, 0.6; EIMS: 174 (M^+, 65.4%).

As indicated in the table, enolizable carbonyl compounds and nonenolizable carbonyl compounds reacted equally well. The experimental procedure for enolizable compounds differs, however, in that it is essential to preform the ylide prior to addition of the carbonyl compound. This is done simply by heating the NaH/phoshonium salt/THF suspension at 62°C for 10 hours before adding the carbonyl compound. In a representative procedure, a suspension of NaH (220 mg, 4.59 mmol, 50% oil dispersion prewashed with hexane) and cyclopropyltriphenylphosphonium bromide (1.76 g, 4.59 mmol) in 15 mL THF was heated at 62°C for 10 hours. A solution of cyclododecanone (644 mg, 3.53 mmol) and TDA-1 (114 mg, 10 mol %) in 5 mL THF was then added to the heated orange suspension. The resulting tan mixture was stirred at 62°C until TLC analysis showed no

TABLE

Entry	Carbonyl Compound	Product	Yield[a]
1			83
2			83
3			54
4			75
5			85
6			95
7			59
8			85

[a] All yields refer to isolated materials, purified by silica gel chromatography.

remaining cyclododecanone. The reaction mixture was then cooled, diluted with pentane (100mL), and passed through a short pad of silica gel. Evaporation of the solvent yielded pure cyclopropylidenecyclododecane (393 mg, 54%) : ^{1}H NMR (300 MHz, $CDCl_3$): 2.25-2.12 (bs, 4H), 1.63-1.50 (m, 4H), 1.40-1.15 (m, 14H), 1.0 (s, 4H); IR (neat): 3050, 2920, 2860, 1470, 1445, 995 cm^{-1}; ^{13}C NMR (100MHz, $CDCl_3$): 126.1, 115.8, 32.3, 24.6, 24.3, 24.2, 23.6, 22.4, 2.1; EIMS: 206 (M^+, 10.9%).

In summary, we have described a method for improving the yields in Wittig reactions involving cyclopropylidenetriphenylphosphorane (**3**), using the phase-transfer catalyst, TDA-1. The simplicity of the operation, the commercial availability of the starting phosphonium salt, and the high yields of alkylidenecyclopropanes obtained relative to other reported procedures make this variation especially attractive for the introduction of the cyclopropane moiety into organic substrates.

ACKNOWLEDGMENT This work was supported by NIH Grant CA37005.

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