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Scalable Preparation of Methylated Ando-Type Horner−Wadsworth−Emmons Reagent

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Supporting Information

ABSTRACT: The Horner−Wadsworth−Emmons (HWE) reactions are vital to the chemical synthesis of complex molecules, forging a carbon−carbon double bond in the generation of α,β-unsaturated enoates from aldehydes or ketones. Despite their frequent use, the *Z*-stereoselective formation of α,β-unsaturated esters from aldehydes have been mostly limited to the use of the commercially available Still−Gennari reagent. Ando developed an alternative reagent to achieve the same formation with less expensive reagents. However, an α-methylated Ando-HWE reagent has remained difficult to prepare, hindering a reliable route to α,β-disubstituted *Z*-enoates. Here, we report the development of a preparative synthesis of a methylated Ando-HWE reagent for the highly *Z*-selective HWE reaction. Costing $0.49/mmol, this synthesis is significantly cheaper than the currently available Still−Gennari reagent ($11/mmol, Millipore Sigma 2018). The purification procedure does not require chromatography, with recrystallization as the only purification method, making it highly amenable to large-scale production.

KEYWORDS: *olefination, Wittig reactions, synthetic methods, alkylation, Horner−Wadsworth−Emmons reaction*

INTRODUCTION

Methods for generating new carbon−carbon bonds are powerful reactions that are widely used in the synthesis of complex molecules. The Horner−Wadsworth−Emmons (HWE) olefination has found widespread use in generating predominantly *E*-α,β-unsaturated esters from aldehydes. The generation of a *Z*-enoate has been more difficult, but two types of reagents have been developed to obtain this selectivity: the Still−Gennari reagent, (2,2,2-trifluoroethyl)phosphonoester **1a**[1] and Ando-type reagents, bis(*O*-aryl)phosphonates **1b**.[2] As shown in Scheme 1, α-alkylation of these types of reagents (step 1) followed by an HWE reaction (step 2) will generate trisubstituted *Z*-α,β-unsaturated systems **3**. These enoates are ubiquitous in synthetic organic chemistry, because they are versatile synthetic intermediates.[3−23]

While highly selective for generating the *Z*-olefin, the commercially available Still−Gennari reagent **1a** is less desirable for large-scale reactions due to its high cost ($11/mmol, Millipore Sigma 2018). The best multigram synthesis of this reagent requires three steps (77% overall yield), one of which requires column chromatography.[24] The preparation of this reagent costs $1.00/mmol, even without including the cost of purification. Alternatively, the Ando group developed reagent **1b** using electron-withdrawing aryloxy groups on the phosphorus atom, which presumably accelerate the formation of a *cis* oxaphosphetane, leading to formation of the *Z*-olefin with high stereoselectivities.[2] These bis(*O*-aryl)phosphonates and their associated reagents cost less to prepare, and the preparation is scalable. Touchard exploited the wide availability of phenols to develop phosphonate **1c**, which could be isolated in a pure form as a solid.[25,26] α-Alkylation of these reagents has been demonstrated with several examples in DMSO using NaH and haloalkanes; however, these reactions typically proceed with modest yields (∼65%) and require column chromatography.[27,28] Despite poor synthetic accessibility, these α-alkylated reagents demonstrated similar *Z*-selectivity as the unsubstituted bis(*O*-aryl)phosphonates in the HWE reaction.

To harness the HWE reaction as a reliable route to trisubstituted *Z*-α,β-unsaturated enoates, it is necessary to develop a method to selectively monoalkylate phosphonates such as **1c**. In this manuscript, we report a scalable and inexpensive method for the preparation of the α-substituted phosphonate **2c** for *Z*-selective olefination reactions.

RESULTS AND DISCUSSION

To develop the required monoalkylation method, phosphonate **1c** was prepared according to the literature.[25] The two unsolved problems were the chemoselectivity for the formation of compounds **2c** and **4** and the overall yield of the reaction. A series of bases, solvents, and additives were screened to determine the optimal conditions to maximize formation of **2c**. Treatment of **1c** with MeI and NaH in DMF led to a mixture of the starting material, the desired monomethylated product **2c**, and the undesired dimethylated product **4** as previously noted by Ando (run 1, Table 1).[27] The use of DBU gave a better chemoselectivity between **2c** and **4**, but only with 67% conversion (run 2). To activate MeI, we tested $AgNO_3$ (run 3) and Ag_2O (run 4) and found that the latter was more efficient, providing a mixture of **2c** and **4** in 92% conversion with a ratio of 93:7.

Because $AgNO_3$ and Ag_2O cost $408/mol and $525/mol (Millipore Sigma), respectively, we decided to revisit NaH ($6/mol, Millipore Sigma). The observed dimethylation was presumably due to the presence of 2 equiv of NaH. As run 1 in Table 2 shows, despite a high ratio of **2c**:**4** (95:5), the conversion from the starting material was only 49%. The

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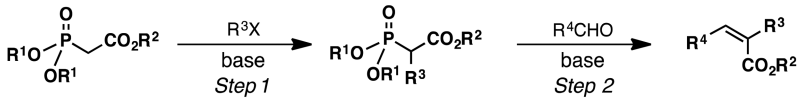
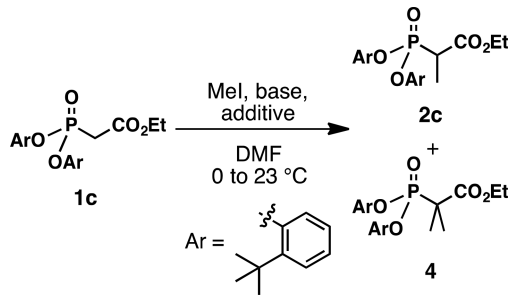
Scheme 1. General Approach for the Preparation of 3



1a: $R^1 = CH_2CF_3$, R^2 = Me
1b: R^1 = Ph, R^2 = Et
1c: R^1 = 2-^{t}BuPh, R^2 = Et

Table 1. Initial Optimization for the Preparation of 2c in DMF



run	base (2 equiv)	additive (1 equiv)	time (h)	conversion (%)[a]	Ratio (2c:4)[a]
1	NaH	none	5	90	64:36
2	DBU	none	3	67	98:2
3	DBU	$AgNO_3$	2.5	70	98:2
4	DBU	Ag_2O	0.7	92	93:7

[a]Determined by the ^{1}H NMR analyses of the crude mixtures.

Table 2. Screening Bases and Solvents for the Preparation of 2c

run	base (equiv)	solvent	temp (°C)	conversion (%)[a]	2c:4[a]
1	NaH (1.0)	DMSO	15	49	95:5
2	NaH (1.0)	THF	15	81	80:20
3	K_3PO_4 (1.1)	MeCN	0→23	30	100:0
4	K_3PO_4 (2.0)	MeCN	0→23	43	100:0
5	KO^{t}Bu (1.0)	DMSO	0→23	78	90:10
6	KO^{t}Bu (1.5)	THF	0→23	91	66:34
7[b]	KO^{t}Bu (1.5)	THF	0→23	92	82:18
8	DBU (1.0)	THF	0	31	100:0
9	DBU (2.0)	THF	0	52	100:0
10[c]	DBU (2.0)	THF	0	53	79:21

[a]Determined by the ^{1}H NMR analyses of the crude mixtures. [b]The reverse addition was employed. [c]LiCl (1.0 equiv).

conversion with NaH was improved by switching the solvent to THF, but at a cost of reduced selectivity (run 2), presumably due to the lack of kinetic preference for deprotonation between **1c** and **2c** with the nondiscriminatory NaH. Thus, we turned our attention to other bases. With the milder base, K_3PO_4, which was used for the α-alkylation of diethylmalonate in the literature,[29] the conversions were poor even with excess base (runs 3 and 4). To exploit sterics to discriminate between the deprotonation of **1c** and **2c**, we turned to bulkier base KO^{t}Bu ($13/mol, Millipore Sigma). When this base was used in DMSO, the conversion improved to 78% (run 5). Switching the solvent from DMSO to THF further improved the conversion at the expense of increased dimethylation (run 6), the origin of which may require further study. Optimization of these conditions revealed that distilling THF prior to use was unnecessary. More importantly, unlike runs 1−6 in which MeI was added to the premixture of phosphonate **1c** and KO^{t}Bu, the addition of KO^{t}Bu as a solid to a solution of **1c** and MeI in THF at 0 °C produced the best yield of **2c** (92% conversion) with synthetically useful chemoselectivity (run 7). The chemoselectivities shown between run 6 and run 7 may be explained by the methylation of **1c** or **2c** at different rates and the kinetic preference for the deprotonation of **1c** over **2c** with KO^{t}Bu. Addition of a solution of KO^{t}Bu in THF was also beneficial in a small scale; however, this became unpractical at scale due to solubility issues. While KO^{t}Bu provided acceptable reaction conversions (92%), the 82:18 ratio of products is less than desirable. We decided to revisit DBU as it provided superior selectivity in DMF (Table 1, run 2) and was expected to achieve a similar trend in THF. Unfortunately, the use of DBU in THF led to poor conversions (31%; run 8), albeit perfect selectivity (100:0). Doubling the amount of DBU improved the conversion, but the efficiency was still below synthetically useful levels (run 9). To improve the conversion efficiency, we sought to activate the starting material by using lithium ions to enhance the acidity similar to the Masamune−Roush protocol.[30] The addition of LiCl did not lead to increased conversion but did decrease the selectivity, indicating the methylated product **2c** was being activated, leading to overalkylation (run 10). Other reagents (e.g., NaCl, KCl) showed no effect on conversion or selectivity (data not shown).

Next, we hypothesized that a sequential combination treatment might yield the desired results. We first treated a solution of phosphonate **1c** and MeI (1 equiv) in THF with KO^{t}Bu (1 equiv) to give a mixture that resulted in 74% conversion and 92:8 selectivity, and then added DBU (2 equiv) and more MeI (1 equiv) to achieve 86% conversion and 91:9 selectivity. After aqueous workup and extraction, the resulting crude material could be recrystallized without column chromatography to give the monomethylated phosphonate **2c** in 67% yield and 87% purity. This procedure was carried out on a 1-mol scale without loss of selectivity, demonstrating its scalability. The sequential combination procedure was also performed using K_3PO_4 instead of DBU to achieve 80% yield with 79% purity after recrystallization. Unfortunately, while the use of K_3PO_4 is more desirable than DBU due to lower cost and simpler workup (e.g., less byproducts in the organic layers), the conversion was lower and overall purity of **2c** with this method was 8% less than that using DBU when scaled up to 100 g scale, with the difference being a larger remaining amount of **1c**. More efforts into optimization of the recrystallization might improve the separation to make this method more synthetically useful.

While similar alkylated Ando-type reagents have demonstrated high *Z*-selectivity in the HWE reaction, phosphonate **2c** has appeared only once in previous literature; however, the authors reported no synthetic experimental information.[31] We decided to evaluate the generality of the *Z*-selectivity of

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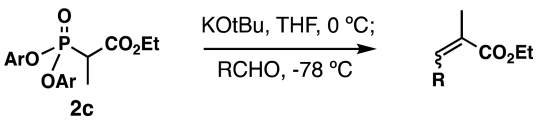
phosphonate **2c** with various aldehydes commonly used to test similar olefination reagents. These results are summarized in Table 3. Compound **2c** shows comparable *Z*-selectivity to the nonalkylated **1c**[25] and related alkylated reagents[27] with near-perfect selectivity with aromatic (Table 3, run 1) and branched (runs 2 and 3) aldehydes and lower selectivity with conjugated and linear substrates (runs 4 and 5). The yields for the more challenging substrates were lower than those from the literature[25,27] due to the shorter times.

Table 3. HWE Reactions of 2c with Aromatic/Aliphatic Aldehydes in THF



run	RCHO	time (h)	yield (%)[a]	ratio (*Z*/*E*)[a]
1	PhCHO	3	94	97:3
2	$^{c}C_6H_{11}CHO$	3	36	94:6
3	^{n}BuCH(Et)CHO	3	60(brsm)	100:0
4	$^{n}C_7H_{15}CHO$	3	84	86:14
5	^{i}PrCH=CHCHO	3	69	70:30

[a]Determined by the ^{1}H NMR analyses of the crude mixtures.

In conclusion, we have developed a method to prepare phosphonate **2c** in high yield and chemoselectivity. The procedure is devoid of column chromatography and does not require expensive reagents. The preparation of phosphonate **2c** from PCl_3 costs $0.49/mmol including all reagents and solvents. The use of commercial THF without distillation further simplifies the procedure. This reagent demonstrated high *Z*-selectivity in the HWE reaction with several aldehydes.

EXPERIMENTAL SECTION

Nondistilled THF (250 mL; water <0.008%) was added to a 1-L round-bottom flask under a nitrogen atmosphere. Phosphonate **1c** (105.42 g, 243.76 mmol) was added to the flask, and the resulting reaction mixture was cooled to 0 °C on ice. The mixture was then treated with MeI (15.10 mL, 243.75 mmol) in one portion at 0 °C. The reaction mixture was kept at 0 °C while KO^{t}Bu (27.35 g, 243.75 mmol) was added slowly to the flask in small portions (**Caution: exothermic**). The resulting mixture was allowed to stir for 1 h at 23 °C. The reaction was cooled to 0 °C, and DBU (72.50 mL, 487.50 mmol) was added slowly, followed by MeI (15.10 mL, 243.75 mmol). The resulting slurry was allowed to stir for 1 h at 23 °C. The reaction was cooled to 0 °C and quenched using saturated aqueous NH_4Cl (200 mL), THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (1 × 200 mL) and dried over Na_2SO_4. The organic layers were then filtered through a cotton plug, and the organic solvents were evaporated under reduce pressure to yield a pale-yellow oil (108.45 g, quantitative yield, 78% purity by ^{1}H NMR analysis). The material was recrystallized from hot hexanes to yield white crystals (72.7 g; 87% purity by ^{1}H NMR).

R_f = 0.34 (20% EtOAc in hexanes); mp = 70−72 °C; IR (film): ν_{max} = 3460, 3083, 2960, 2872, 1741 (C=O), 1488, 1442, 1300 (P=O), 1257, 1182, 1087, 1055, 945, 757 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, $CDCl_3$): δ 7.73 (app d, *J* = 8.1 Hz, 1H; *Ar*), 7.64 (app d, *J* = 8.1 Hz, 1H; *Ar*), 7.34−7.31 (app m, 2H; *Ar*), 7.14−7.02 (m, 4H; *Ar*), 4.14 (dq, *J* = 10.7, 6.9 Hz, 1H; CH_2CH_3), 4.00 (dq, *J* = 10.7, 6.9 Hz, 1H; CH_2CH_3), 3.47 (dq, *J* = 24.0, 7.2 Hz, 1H; P(O)CHCH$_3$), 1.68 (dd, *J* = 19.5, 7.2 Hz, 3H; P(O)CHCH_3), 1.35 (s, 9H; ^{t}*Bu*), 1.31 (s, 9H; ^{t}*Bu*), 1.08 (t, *J* = 6.9 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, 293 K, $CDCl_3$): 168.4 (d, *J* = 4 Hz), 151.0 (d, *J* = 10 Hz), 150.6 (d, *J* = 9 Hz), 138.9 (d, *J* = 4 Hz), 138.8 (d, *J* = 4 Hz), 127.5, 127.5, 127.3, 127.3, 124.4, 124.3, 119.8 (d, *J* = 3 Hz), 119.6 (d, *J* = 3 Hz), 61.9, 41.7 (d, *J* = 138 Hz), 34.7, 30.2, 30.09, 13.8, 12.0 (d, *J* = 6 Hz) ppm; HRMS (ES+) calcd for $C_{25}H_{35}O_5P$ $[M + H]^{+\cdot}$ 447.22949, found 447.23151.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00423.

^{1}H and ^{13}C NMR spectra for compound **2c** (PDF)

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Notes

The authors declare no competing financial interest.

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