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One-Pot (1-Ethoxycarbonylcyclopropyl)-triphenylphosphonium Tetrafluoroborate Ring-Opening and Wittig Reaction

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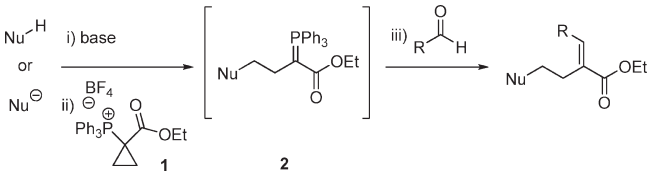
ABSTRACT



An efficient method was developed for the synthesis of 2-methylene-4-substituted ethyl butyrates via cyclopropyl opening followed by a Wittig reaction. The desired products were formed in a two-step, one-pot reaction sequence. Alternatively, the key intermediate ylide 2 was isolable and could be stored under oxygen-free conditions and subsequently utilized. A variety of nucleophiles were found to open the commercially available cyclopropane 1. The resulting ylide reacted with aldehydes to provide *E*-olefinic products.

In practice, the (1-ethoxycarbonylcyclopropyl)triphenylphosphonium tetrafluoroborate **1** has been widely used to form carbocyclic and heterocyclic compounds.[1] In the reported examples, the cyclopropane opens with nucleophiles to provide an intermediate ylide that subsequently undergoes an intramolecular Wittig reaction to form cyclic systems. In this work, we report a novel application of this reagent, a one-pot, tandem ring-opening Wittig sequence. We adapted this methodology for our purpose by reacting the intermediate ylide in an intermolecular fashion to provide 2-methylene-4-substituted butyrates.

Here, we react commercially available **1** with a number of nucleophiles followed by the addition of unhindered aldehydes to provide highly substituted butyrates with good efficiency and operational ease. Various nucleophiles have been employed to open the (1-ethoxycarbonylcyclopropyl)triphenylphosphonium salt to form the ylide.[1a–f] Reactions were monitored by LC–MS, as both intermediate ylide **2** and final product **3** were easily detected in the two-step, one-pot reaction (Figure 1).

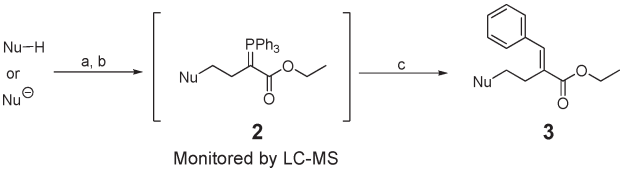


Figure 1. General one-pot reaction: (a) deprotonation, (b) opening of (1-ethoxycarbonylcyclopropyl)triphenylphosphonium tetrafluoroborate, (c) Wittig reaction.

To establish a general method, 3,4,5-trimethylpyrazole was selected as a trial nucleophile for optimization in combination with various bases (NaH, LiHMDS, K_2CO_3/NaOH/TBAHS)[2] and solvents (THF, toluene, DMF) (Table 1).

The best yield of compound **4** was obtained when sodium hydride in either THF or toluene was used.

(1) (a) Fuchs, P. L. *J. Am. Chem. Soc.* **1974**, *96*, 1607. (b) Dauben, W. G.; Hart, D. J. *Tetrahedron Lett.* **1975**, *49*, 4353. (c) Flitsch, W.; Pandl, K.; Russkamp, P. *Liebigs Ann. Chem.* **1983**, *4*, 529. (d) Flitsch, W.; Russkamp, P. *Liebigs Ann. Chem.* **1983**, *4*, 521. (e) Barreau, M.; Ponsinet, G. *Tetrahedron Lett.* **1985**, *26*, 5451. (f) Chatterjee, P.; Murphy, P. J.; Pepe, R.; Shaw, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, *17*, 2403. (g) Hersperger, R.; Janser, P.; Pfenninger, E.; Wuethrich, H. J.; Miltz, W. Int. Pat. Appl. 077932, 2005.

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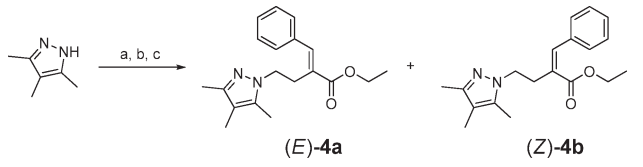
Table 1. Solvent and Base Selection for the One-Pot Synthesis[a]



entry	solvent	base	*E*/*Z* ratio	isolated yield (%)
1	THF	NaH	1:0	60
2	toluene	NaH	1:0	57
3	DMF	NaH	1:0	47
3	THF	LiHMDS	1:0	32
4	toluene	LiHMDS	1:0	34
5	DMF	K_2CO_3/NaOH/TBAHS		0

[a] Reaction conditions: (a) base/solvent/20 °C/30 min; (b) (1-carbethoxycyclopropyl)triphenylphosphonium tetrafluoroborate/solvent/80 °C/2 h; (c) benzaldehyde/solvent/80 °C/overnight.

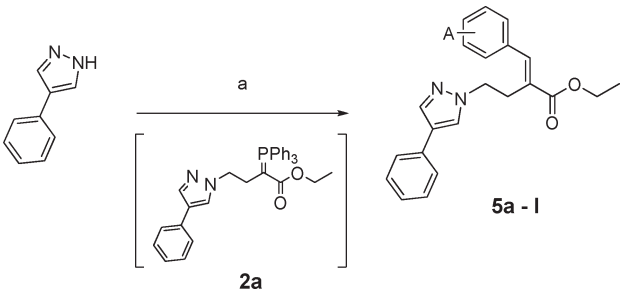
Notably, the (1-ethoxycarbonylcyclopropyl)triphenylphosphonium salt does not form the desired ylide **2** with the sodium salt of trimethylpyrazole at room temperature, so moderate heating is required. In addition, the reaction with LiHMDS resulted in diminished yields of isolated product. The K_2CO_3/NaOH/TBAHS[2] base system did not result in the desired ylide **2**, even after overnight reaction (via LC−MS), and did not provide the desired product **4**. This optimization showed that either THF or toluene with NaH provides useful yields of butyrates. Interestingly, in each case, only a single olefin isomer was detected in crude product NMR spectra. After isolation of the product, the olefin geometry was shown by an NOE experiment to have an *E*-configuration (**4a**), which is consistent with recently published work.[3]

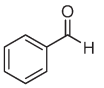
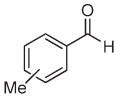
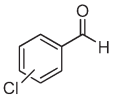
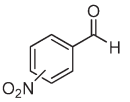
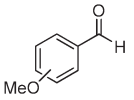
The electronic and steric influence of aldehyde substituents on the reaction outcome was examined using 4-phenylpyrazole as the nucleophile (Table 2).

In order to minimize variability between experiments, we opted to utilize the isolated ylide **2a**, which was synthesized on a multigram scale (Supporting Information). Electron-donating methoxy groups on the benzaldehyde gave poorer yields when compared to the other benzaldehyde analogues tested, irrespective of the position of the methoxy group on the aryl ring. The most significant influence was observed when the methoxy group was in the ortho position, suggesting sterics may also play a role in the reaction outcome (entry 5, Table 2).

Electron-withdrawing groups on the benzaldehyde, such as chloro and nitro, provided products in excellent yield with no detrimental influence of ortho-substitution (entries 3 and 4). The *o*-methyl benzaldehyde, however, did result in a reduced yield compared to its meta and para counterparts (entry 2, Table 2). In all cases, the *E*-olefin

Table 2. Electronic Effect vs Steric Hindrance[a]



entry	aldehyde	position	yield (%)
1			91
2		*p*-methyl	80
		m-methyl	75
		o-methyl	56
3		*p*-chloro	82
		m-chloro	83
		o-chloro	86
4		*p*-nitro	90
		o-nitro	83
5		*p*-methoxy	43
		m-methoxy	43
		o-methoxy	32

[a] Reaction conditions: (a) preformed ylide **2a**/aldehyde/toluene (2 mL)/80 °C/overnight, (0.1 M).

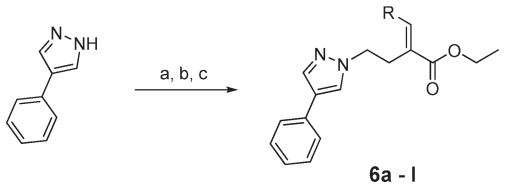
geometry was the only isomer observed. Interestingly, the p-nitro analogue (entry 4, Table 2) provided the *E*-olefin isomer initially, but upon standing slow olefin isomerization was observed.

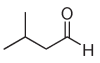
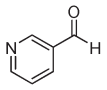
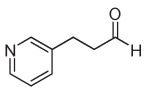
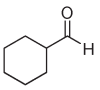
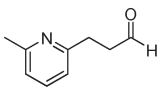
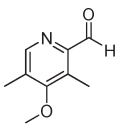
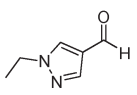
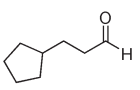
Heterocyclic and aliphatic aldehydes were next investigated to further test the reaction scope using the stepwise, one-pot method described above (Table 3). Not surprisingly, formaldehyde reacted effectively with the ylide **2a** to provide desired product (Table 3, entry 1). Formaldehyde could be introduced either as *p*-formaldehyde or as an aqueous solution of formaldehyde with equal effectiveness. The pyridyl and pyrazolyl aldehydes (entries 2 and 6 Table 3) provided products in moderate yield. Homologues of the pyridyl aldehyde (entries 3 and 4, Table 3) provided products in moderate yield, suggesting that alkyl aldehydes might also provide products. The steric encomberance of the aldehyde in entry 5, possibly along with electronics, effectively combined to prevent the reaction. Along with aliphatic aldehydes, steric hindrance seems to have a major influence, since good yields were observed

(2) (a) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617. (b) Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531.

(3) Appel, R.; Loos, R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 704.

Table 3. Phenylpyrazole Nucleophile with Variety of Aldehydes[a]



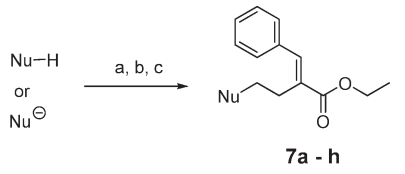
entry	aldehyde	yield (%)	entry	aldehyde	yield (%)
1		85	7		53
2		50	8		0
3		50	9		0
4		27	10		10
5		0	11		55
6		36	12		90

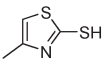
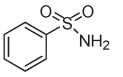
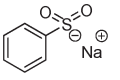
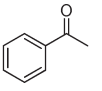
[a] Reaction conditions: (a) NaH/THF/20 °C/30 min; (b) (1-carbethoxycyclopropyl)triphenylphosphonium tetrafluoroborate/THF/80 °C/2 h; (c) aldehyde/80 °C/overnight.

when less encumbered aldehydes were employed (entries 7, 11, and 12, Table 3). Little or no product forms with more bulky aliphatic side chains (entries 8–10, Table 3), and heating to 160 °C in DMF was ineffective at increasing product formation. Likewise, we had no success with ketones as Wittig partners.[4] From a practical standpoint, product separation from starting aliphatic aldehyde and triphenylphosphine oxide was challenging when 4-phenylpyrazole was utilized as the nucleophile, resulting in reduced isolated yields for entries 2, 6, 10, and 11, even when scavenging resins were used to remove triphenylphosphine oxide.[5]

Finally, we examined a variety of nucleophiles for opening the cyclopropane ring in **1** (Table 4). For each of the nucleophiles, the two-step, one-pot reaction gave approximately 50–70% isolated yield of desired product. Four different classes of nitrogen-based nucleophiles (entries 1, 2, 4, and 6, Table 4) were successfully employed. They ranged from morpholine and azide to a benzenesulfonamide anion and clearly demonstrated the diversity of reactants capable of providing substituted butyrate products. A single oxygen nucleophile was employed in the form of phenol, and it provided a moderate yield of product (entry 3, Table 4). Finally, two different sulfur nucleophiles were tested, a sulfinic acid and a thiol (entries 5 and 7, Table 4), and both provided the desired product in useful quantities. The benzenesulfonamide in entry 6 (Table 4) was successful but was also found to react further to give a cyclized lactam product as a 3:1 ratio (linear to lactam) by LC–MS (Scheme 1).[6] However, the described linear product could be isolated by careful chromatography.

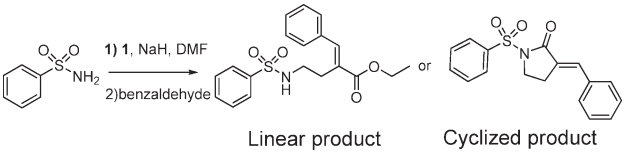
Table 4. Various Nucleophiles with Benzaldehyde[a,b]



entry	nucleophile	yield (%)	entry	nucleophile	yield (%)
1		85	5		57
2		57	6		55*
3		47	7		50
4	N_3Na	53	8		0

[a] Reaction conditions: (a) NaH/THF or toluene/0 °C/30 min; (b) (1-carbethoxycyclopropyl)triphenylphosphonium tetrafluoroborate/THF or toluene/80 °C/2 h; (c) benzaldehyde/THF or toluene/80 °C/overnight. [b] See Scheme 2 for details.

Scheme 1. Linear vs Cyclized Product of Sulfonamide

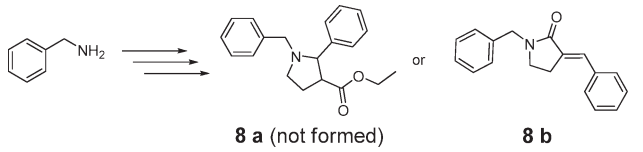


Unlike the other examples in Table 4, the sulfonamide has two potentially acidic protons and provided two products from the reaction in THF. When the reaction was carried out with less than 1.0 equiv of sodium hydride

(4) (a) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855. (b) Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987.
(5) Lipshutz, B. H.; Blomgren, P. A. *Org. Lett.* **2001**, *3*, 1869.

in THF, only the linear product was formed. However, when greater than 1.0 equiv of sodium hydride (i.e., 1.2 or 2.0 equiv) was used, both linear and cyclized product formed (Scheme 1). Interestingly, when the solvent was changed to DMF, only the linear product was formed regardless of the amount of base utilized. When the isolated linear product was treated with NaH (0.1 equiv) in THF, the cyclized product formed while the same reaction in DMF did not form cyclized product.[6a]

Scheme 2. Application of Reaction



Prompted by the in situ cyclization observed with the benzenesulfonamide to give the lactam, we wanted to explore the generality of this transformation with another nucleophile. Benzylamine was employed as the nucleophile in our typical one-pot reaction (Scheme 2). Benzylamine was heated directly with cyclopropane **1** in DMF at 80 °C to give **8b** in 75% isolated yield.[6c,d] We were unable to detect any of the 5-*endo*-ring product (**8a**) by NMR or LC−MS (details in the Supporting Information).[6a]

Overall, we were able to synthesize 2-methylene-4-substituted ethyl butyrates via a one-pot ring-opening of (1-ethoxycarbonylcyclopropyl)triphenylphosphonium tetrafluoroborate followed by a Wittig reaction. Products were isolated in moderate yield and good purity. We have described general conditions where a variety of nucleophiles generated with THF/NaH provided a product. Furthermore, when appropriate nucleophiles were utilized a clean cyclization to form a pyrrolidinone ring was possible.

Acknowledgment. We thank our colleagues in the Pfizer Antibacterial Chemistry Department for their support of this work.

Supporting Information Available. Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

(6) (a) Ichikawa, J.; Lapointe, G.; Iwai, Y. *Chem. Commun. (Cambridge, U.K.)* **2007**, *26*, 2698. (b) Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801. This molecule is similar to **8b**; see:(c) Iwamoto, K.; Kojima, M.; Chatani, N.; Murai, S. *J. Org. Chem.* **2001**, *66*, 169. (d) Li, S.; Yuan, W.; Ma, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2578.