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Reactivity of Mitsunobu Reagent toward Carbonyl Compounds

Ryan D. Otte, Tomoyo Sakata, Ilia A. Guzei, and Daesung Lee*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

dlee@chem.wisc.edu

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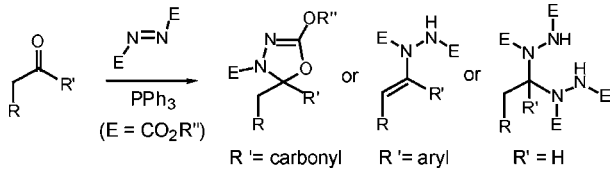
ABSTRACT

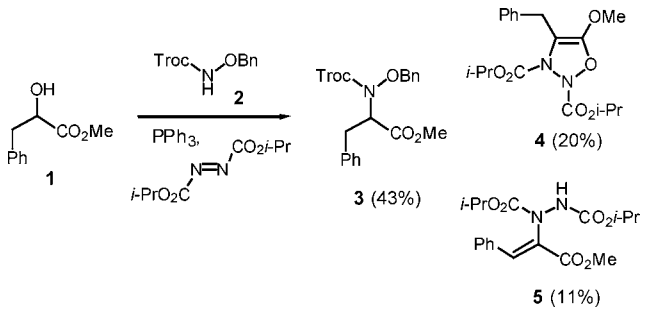


The nitrogen-based nucleophile generated from azodicarboxylate and triphenylphosphine displayed an excellent reactivity toward carbonyl compounds to generate a variety of different final products depending on the substituent pattern on the carbonyl carbon. From the structures of these adducts, a straightforward mechanistic interpretation for the formation of different products is provided.

The Mitsunobu reaction is a versatile synthetic method mainly involved in the transformation of C−OH to C−X bond (X = O, N, S, C) with either inversion or retention of stereochemistry.[1] In general, the outcome of this reaction is very reliable and straightforward, but unexpected results were often observed probably due to the side reactions that involve the oxidation of the substrate alcohol to carbonyl compounds followed by their subsequent reaction.[2] Notwithstanding the participation of the carbonyls in the Mitsunobu reaction, the reaction between carbonyls and the nucleophilic species known as the Morrison−Brunn−Huisgen betaine[3] generated from $R_2OCN{=}NCO_2R$ and PR'_3 has not been studied thoroughly. Only recently Liu and co-workers reported the synthesis of vinyl hydrazines from simple ketones under Mitsunonu conditions.[4]

In the reaction between alcohol **1** and **2** to form **3** under typical Mitsunobu conditions, unexpected transformations (**1** to **4** and **5**) were observed by Miller and Kolasa (Scheme 1).[2]

Scheme 1



In their report, a mechanistic rationale was provided on the basis of an unusual sequence of bond-forming processes

(1) Reviews: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. Mechanistic studies (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (d) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. (e) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (f) Wilson, S. R.; Perez, J.; Pasternak, A. *J. Am. Chem. Soc.* **1993**, *115*, 1994. (g) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967. (h) Watanabe, T.; Gridnev, I. D.; Imamoto, T. *Chirality* **2000**, *12*, 346. (i) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751. (j) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4051. (k) Dinsmore C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885. For the development of new Mitsunobu reagents, see: (l) Tsunoda T, Ito, S. *J. Synth. Org. Chem. Jpn.* **1997**, *50*, 631.

(2) (a) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978. (b) Kurihara, T.; Sugizaki, M.; Kime, I.; Wada, M.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2107.

(3) Satish Kumar, N.; Praveen Kumar, K.; Pavan Kumar, K. V. P.; Kommana, P.; Vittal, J. J.; Kumara Swamy, K. C. *J. Org. Chem.* **2004**, *69*, 1880.

(4) (a) Liu, Y.; Xu, C.; Liu, L. *Synthesis* **2003**, 1335. For other vinylhydrazine dicarboxylates synthesis, see: (b) Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129. (c) Lee, C. B.; Newman, R. J. J.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161. (d) Bloch, J. C. *Tetrahedron* **1969**, *25*, 619.

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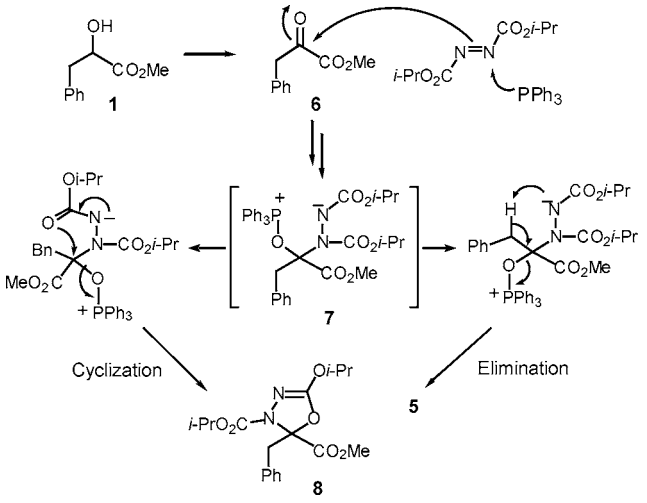
Scheme 2

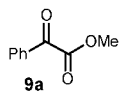
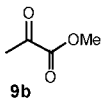
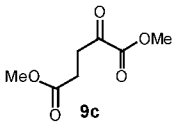
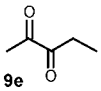
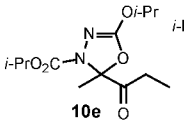
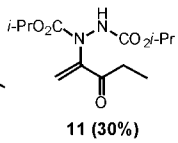
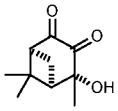
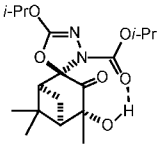


in combination with spectroscopic evidence to support the identity of products **4** and **5**. Intrigued by this observation, we systematically studied the reactivity of the Morrison−Brunn−Huisgen betaine toward carbonyl compounds possessing different electronic and steric environments. Herein we wish to report the general reactivity profile of this betaine leading to different end products and the associated mechanistic rationale.

We suspected that the unexpected products **4** and **5** should be derived from a common intermediate that contains the ketone oxidation state at the α-carbon to the ester functionality. As shown in Scheme 2, the starting alcohol **1** was first oxidized under the conditions to the corresponding ketone **6**, which then underwent a nucleophilic addition by a nitrogen nucleophile generated from azodicarboxylate and triphenylphosphine (PPh_3) to give a penultimate intermediate **7**. The influence exerted by the substituents on **7** will then determine its fate, thereby leading to either an intramolecular S_N2 process to give **8**[5] (not **4**) or an E2-like elimination[6] process to give **5**. Therefore, we decided to employ α-ketoesters and α-diketones as the substrates to examine the addition reaction of the Mitsunobu reagent to the activated carbonyl[3] group.

Gratifyingly, a clean conversion of α-ketoesters **9a**−**c** and α-diketones **9d**−**f** was observed to give a 1:1 adduct between substrates and azodicarboxylate when treated with diisopropyl azodicarboxylate (DIAD) and PPh_3 (Table 1). Substrate **9a** afforded a single product in 90% yield (entry 1). Based on the spectroscopic characteristics of this compound as well as the mechanistic consideration depicted in Scheme 2, we assigned the compound as **10a**, the structure of which was confirmed by X-ray diffraction analysis (Figure 1). Dibenzyl azodicarboxylate (DBAD) and PPh_3 gave a similar product **10a′** (71%) differing only by the alkyl group on the azodicarboxylate (entry 2). Methyl pyruvate **9b** gave **10b**[7] and **10b′** from the reaction by DIAD or DBAD together with PPh_3 in 86% and 83% yields, respectively. Additional ester functionality on the substrate did not interfere with the reaction, therefore **9c** afforded **10c** in 93% yield. α-Diketone **9d** reacted only with one carbonyl group even in the presence of excess reagents to provide **10d** and **10d′** in 72% and 55%

Table 1. Reactions of Mitsunobu Reagent with α-Ketoesters and α-Diketones[a]

entry	ketone (**1**)	product (**2**)	yield (%)
1		**10a** (R = *i*-Pr)	90
2	**9a**	**10a'** (R = Bn)	71
3		**10b** (R = *i*-Pr)	86
4	**9b**	**10b'** (R = Bn)	83
5	 **9c**	**10c**	93
6		**10d** (R = *i*-Pr)	72
7	**9d**	**10d'** (R = Bn)	55
8	 **9e**	 **10e**  **11 (30%)**	56
9	 **9f**	 **10f**	79

[a] All reactions were carried out in THF (0.5 M) with azodicarboxylate (1.2 equiv) and PPh_3 (1.5 equiv) at room temperature.

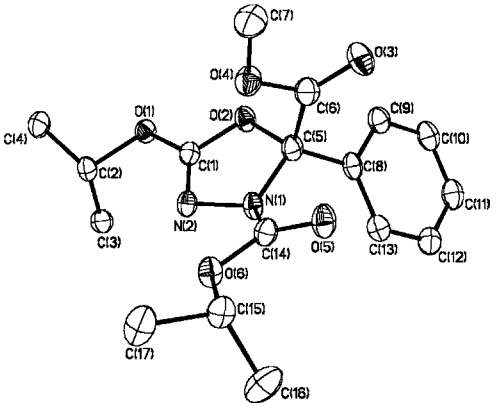


Figure 1. Compound **10a**.

(5) This type of cyclic structure was also generated from a different route; see: Mukaiyama, T.; Atsumi, K.; Takeda, T. *Chem. Lett*. **1976**, 597.

(6) Although an intramolecular proton abstraction is indicated, that does not exclude the intermolecular process.

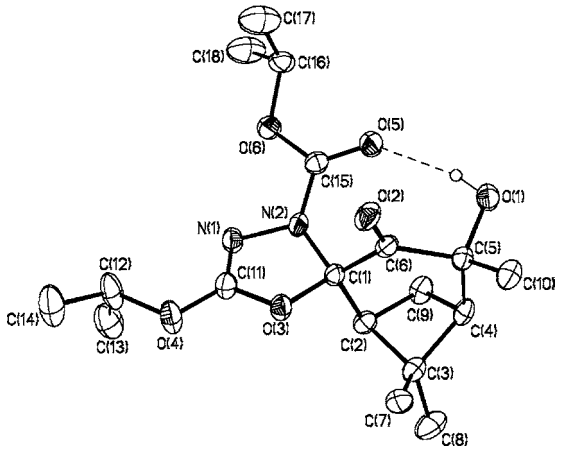


Figure 2. Compound **10f**.

yields. As expected, unsymmetrical α-diketone **9e** reacted on the less hindered carbonyl to yield **10e** as well as an E2 elimination product **11** in 30% yield.[8] At this point it is not clear what causes more facile elimination with **9e** compared to other substrates. A cyclic α-diketone **9f** gave the adduct **10f** uneventfully in 79% yield even in the presence of the hydroxyl group. The single-crystal X-ray analysis confirms the regio- and stereochemical consequence of **10f** (Figure 2). However, the stereochemistry at the newly formed quaternary center is the opposite to the expected configuration based on the initial addition of the nitrogen nucleophile from the sterically less hindered face of the carbonyl group followed by the inversion during the intramolecular S_N2-type ring closure. This may be the result of thermodynamic equilibrium to place the sterically hindered carboxylate in the same orientation as the methylene bridge and not the *gem*-dimethyl methylene bridge. This eventually allows for hydrogen bonding between the hydroxyl and the carboxylate.

Next, we examined the elimination versus the cyclization selectivity with other types of ketones.[4] Additional selectivity concern was the regioselectivity if elimination occurred from the intermediate derived from unsymmetical ketones and *E*/*Z* selectivity of the resultant enamine-like double bond if the substrates are not methyl ketones.

Unsymmetrical acyclic ketones **12a**−**b** provided single regioisomers **13a**−**b** in 86% and 69% yield respectively (Table 2) when treated with DIAD and PPh_3 in THF, which is the consequence of a regioselective E2-like elimination of triphenylphosphine oxide by the proton abstraction from the sterically less hindered carbon in the corresponding intermediate related to **7** (entries 1 and 2). An alkyl alkynyl ketone **12c** provided *E*-isomer selectively (entry 3), the stereochemistry of which was deduced from the NOE experiment of related compounds.[9] Interestingly, under the

Table 2. Reactions of Mitsunobu Reagent with Ketones[a]

entry	ketones	product	yield (%)
1	**12a**	**13a**	86
2	**12b**	**13b**	69
3	**12c**	**13c**	74
4	**12d**	**13d**	48
5	**12e**	**13e**	75
7	**12f**	**13f**	81
8	**12g**	**13g**	50
9	**12h**	**13h**	54
10	**12i**	**13i**	83
11	**12j**	**13j**	75
12	**12k**	**13k**	60

[a] All reactions were carried out in THF (0.5 M) with 1.2 equiv of DIAD and 1.5 equiv of PPh_3 at room temperature.

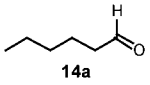
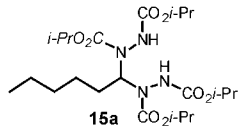
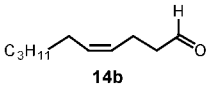
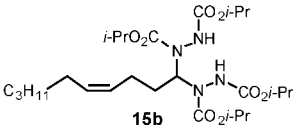
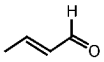
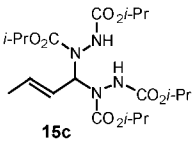
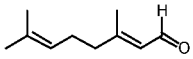
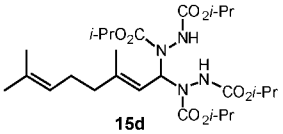
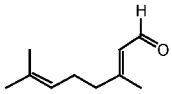
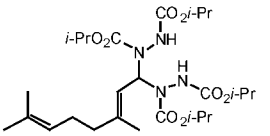
reaction conditions, 1,4-addition to the conjugated alkyne did not occur. Cyclic ketones **12d**−**f** behave similarly to give the elimination products **13d**−**f** in marginal to good yields (entries 4−7). Conjugated enones **13g**−**j** showed a similar behavior to generate 1,3-dienes **13g**−**j** (entries 8−11) in a reasonable range of yields (50−83%).[10] Again, the probable 1,4-addition products were not observed in this reaction. Cyclic conjugated ketone **12k**, possessing only γ-protons to be eliminated, provided a conjugated 1,3-diene **13k** in 65% yield as a single product (entry 12).

(7) The spectroscopic data of **10b** are identical to those of **13b** in ref 2a, one of compounds assigned as **4** possessing methyl instead of benzyl group.

(8) The same type of compounds was synthesized from ethyl vinyl ketone and azodicarboxylate via Morita−Baylis−Hillman reaction; see: Kamimura, A.; Gunjigake, Y.; Mitsudera, H.; Yokoyama, S. *Tetrahedron. Lett.* **1998**, *39*, 7323.

(9) Compound **13i** shows strong NOE between the methyl and a vinyl proton, indicating the stereochemistry shown in the structure.

Table 3. Reactions of Mitsunobu Reagent with Aldehydes

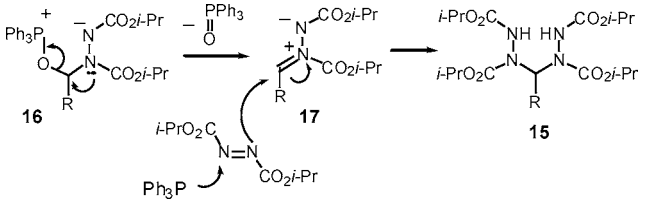
entry	aldehyde	product	yield (%)
1	 **14a**	 **15a**	46
2	 **14b**	 **15b**	46
3	 **14c**	 **15c**	67
4	 **14d**	 **15d**	38
7	 **14e**	 **15e**	70

[a] Reactions with DIAD (1.2 equiv) and PPh_3 (1.5 equiv) in THF (0.5 M) at room temperature. [b] With an excess DIAD and PPh_3.

The reaction of aldehydes **14a**−**e** with Mitsunobu reagent took another course of reaction to generate **15a**−**e**, a 1:2 adduct of aldehydes with azodicarboxylate (Table 3). This is presumably due to the reduced steric hindrance of the putative intermediate **16**, which generates a new intermediate **17** by extruding triphenylphosphine oxide, thereby allowing for an addition of another nitrogen nucleophile (Scheme 3).[11] A similar adduct formation was observed by Liu and coworkers when acetone was used as a carbonyl substrate.[3]

In summary, we have examined and found a general reactivity profile of a variety of carbonyl compounds with the nitrogen nucleophile derived from azodicarboxylate and triphenylphosphine. The different steric and stereoelectronic effects exerted by the substituents on the carbonyl group

Scheme 3



influenced the fate of the reactive intermediate generated along the reaction. The selectivity between several possible reaction manifolds is generally high, thereby providing one major end product. This reaction is a useful synthetic tool to prepare nitrogen-containing olefins. Especially, the reaction of conjugated ketones should be an efficient method for the synthesis of 1,3-dienes containing nitrogen substituents.

Acknowledgment. We thank Wisconsin Alumni Research Foundation and the Dreyfus Foundation for financial support. NSF (CHE-9208463) and NIH (1 S10 RR0 8389-01) for NMR and mass spectrometry instrumentation is greatly acknowledged.

Supporting Information Available: General procedures, characterization of represented compounds, and CIF files for compounds **10a**, **10f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0475008

(10) For other methods for the preparation of 1,3-dienes, see: (a) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, F.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc*. **1993**, *15*, 4403. (b) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242. (c) Benedetti, F.; Pitacco, G.; Valentin, E. *Tetrahedron* **1979**, *35*, 2293. (d) Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M. *J. Chem. Soc., Chem. Commun*. **1985**, *20*, 1375. (e) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett*. **1990**, *31*, 6713. (f) Veronese, A. C.; Morelli, C. F.; Basato, M. *Tetrahedron* **2002**, *58*, 9709. (g) Maas, G.; Mayer, T. *Synthesis* **1991**, 1209. (h) Mass, G.; Brunner, M. *Synthesis* **1995**, 957. (i) Enders, D.; Hecker, P.; Meyer, O. *Tetrahedron* **1996**, *52*, 2909. (j) David, O.; Vanucci-Bacque, C. *Heterocycles* **2004**, *62*, 839.

(11) We appreciate the comment from one of the reviewers, suggesting alternative mechanistic rationale for the formation of different products (**10**, **11**, **13**, **15**) from the common intermediate **8′** due to the stability and reactivity difference caused by the substituent R and R′.