Nucleophilic α-Addition to Alkynoates. A Synthesis of Dehydroamino Acids

Barry M. Trost* and Gregory R. Dake

Department of Chemistry, Stanford University
Stanford, California 94305

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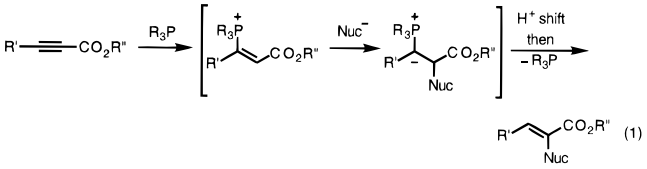
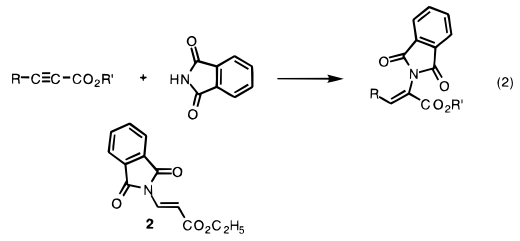
The design of ligands for biological systems to provide increased understanding of function at a molecular level and to open avenues for therapeutic agents has placed increased emphasis on the availability of unusual amino acids and their derivatives.[1] Dehydroamino acids constitute one such class as well as serve as precursors to the saturated amino acids.[2] Increasing the availability of such amino acid derivatives becomes an important goal. The postulation that the phosphine-induced isomerization of alkynoates to 2,4-dienoates[3] and addition of pronucleophiles to the 4-position[4,5] of these substrates suggested the possibility of a new and unprecedented reactivity pattern for alkynoates—nucleophilic addition at the α-position as shown in eq 1 as a new source of dehydroamino acids. In this communication, we record our initial studies that validate this new pattern of reactivity.

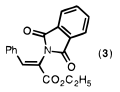
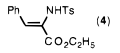
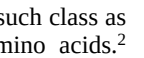
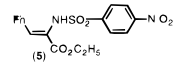
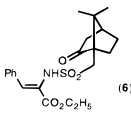
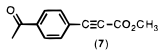
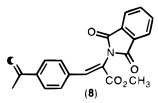
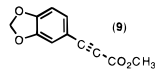
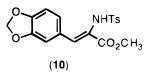


A critical issue to consider in the realization of this new paradigm is the ability of the nucleophile to undergo simple conjugate addition in preference to the α-attack since phosphines could also serve as general base catalysts for Michael additions.[6] Ethyl propiolate should be particularly prone to undergo such Michael additions. Given that the proposed route of eq 1 requires both general acid and base catalysis, a 1:1 sodium acetate−acetic acid buffer was employed. Heating a 1:1 mixture of ethyl propiolate and phthalimide at 105 °C in toluene with 10 mol % triphenylphosphine, 50 mol % acetic acid, and 50 mol % sodium acetate gave a 1:1 adduct in 95% yield (eq 2 and Table 1, entry 1).



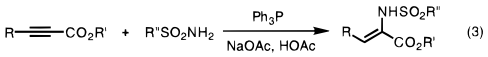
The ^{1}H NMR spectrum immediately reveals that the structure of the adduct must be the α-addition product **1**[7] and not the conjugate addition one **2** since the olefinic signals were two singlets at δ 6.66 and 5.97. Other substrates that cannot undergo isomerization to allenes and 2,4-dienoates and thereby should participate in this reaction are the arylpropiolates. Indeed, ethyl phenylpropiolate (eq 2 and Table 1, entry 2) participated equally well to give a single geometric and regio-isomer **3**,[7] which is also a known compound.[8] The regioselectivity is unambigously established spectroscopically. For both adducts **1** and **3**, the regioselectivity was further verified by catalytic hydrogenation to the phthalimide derivatives of alanine[9a] and phenylalanine,[9b] respectively.

Table 1. α-Addition of Nitrogen Nucleophiles to Conjugated Alkynoates[a]

Entry	Alkynoate	Nucleophile	Time (h)	Product	Isolated Yield
1	HC≡CCO$_2$C$_2$H$_5$		18	 (1)	95%
2	PhC≡CCO$_2$C$_2$H$_5$		18	 (3)	82%
3	PhC≡CCO$_2$C$_2$H$_5$	H_2NTs	18	 (4)	82%
4	PhC≡CCO$_2$C$_2$H$_5$		5	 (5)	57%
5	PhC≡CCO$_2$C$_2$H$_5$		18	 (6)	66%
6	 (7)		18	 (8)	66%
7	 (9)	H_2NTs	18	 (10)	56%

[a] All reactions were run in $PhCH_3$ at 105 °C with 10 mol % Ph_3P, 50 mol % HOAc, and 50 mol % NaOAc.

Sulfonamides also serve as pronucleophiles with the arylpropiolates. Under identical conditions as above, ethyl phenylpropiolate and *p*-toluenesulfonamide gave the α-adduct **4**[10] (eq 3 and Table 1, entry 3). The illustration of the ease of removal of a (*p*-(nitrophenyl)sulfonyl group[11] led us to examine its



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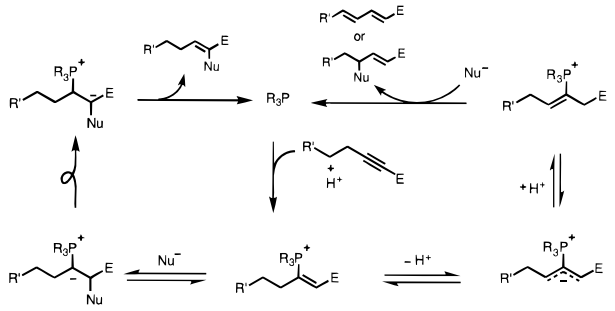
Scheme 1. Competitive Pathways in Phosphine-Catalyzed Nucleophilic Addition



corresponding sulfonamide (eq 3 and Table 1, entry 4). In spite of the ease of reduction of the nitrosulfonamide, reaction proceeds well to give adduct **5**.[7] Table 1, entry 5, illustrates that even aliphatic sulfonamides are good pronucleophiles. This example raises the prospect of a chiral sulfonamide as a chiral auxiliary with respect to additions to the double bond of adduct **6**.[7]

Substituted arylpropiolates also participate in these reactions. The *p*-acetyl group as in **7** led to smooth α-addition (eq 1 and Table, 1, entry 6) to give **8**.[7] Electron rich substituents as in the case of propiolate **9** also serve as partners.

The utilization of alkyl-substituted propiolates suffers from possible competitive γ-addition[4] or redox isomerization[3] to 2,4-dienoates as illustrated in Scheme 1. Methyl 2-heptynoate (**11**) was examined as a model substrate with both imides and sulfonamides as nucleophiles. Equation 4 and Table 2 summarize the effect of reaction parameters on the course of this process. With our standard conditions, the major product was redox isomerization to **14** (Table 2, entry 1). Combination of the phosphine trigger and an acid source as in 2-(diphenylphosphino)benzoic acid (DPPBA) failed to effect any reaction whatsoever (Table 2, entry 2). A phosphite behaved similarly (entry 3). On the other hand, the bidentate phosphine 1,3-bis(diphenylphosphino)propane (dppp) gave the desired α-adduct[7] in the presence of acetic acid (Table 2, entry 4) or, better, in the presence of the sodium acetate−acetic acid buffer (Table 2, entry 5). Under similar conditions, phthalimide led only to redox isomerization (entry 6). Due to the precipitation of sodium phthalimide under these conditions, the low concentration of any phthalimide in solution may be responsible for the failure to capture any of the proposed intermediates. Credence to this suggestion derived from the use of phenol as the acid in which case a homogeneous solution was maintained and a 33% isolated yield of the α-adduct **12**[7] was obtained (eq 4 and Table 2, entry 7). By using the more nucleophilic tetrahydrophthalimide system, no redox isomerization was observed and a 6.7:1 ratio of the α- and γ-adducts[7] was obtained (entry 8).

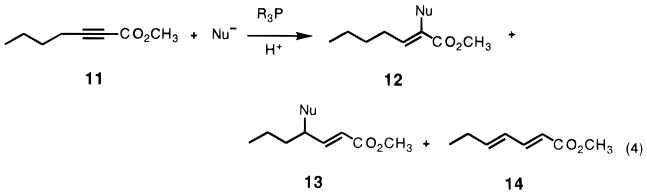


Table 2. Reactions of Methyl 2-Heptynoate[a]

Entry	Nucleophile	Phosphine	Co-Catalyst	% **12**	% **13**	% **14**	Yield
1	$TsNH_2$	Ph_3P	HOAc/NaOAc	12%	—	88%	92%
2	$TsNH_2$	DPPBA	—	—	—	—	0%
3	$TsNH_2$	$(i\text{-}C_3H_7O)_3P$	HOAc/NaOAc	—	—	—	0%
4	$TsNH_2$	dppp	HOAc	100%	—	—	45%
5	$TsNH_2$	dppp	HOAc/NaOAc	76%	—	24%	82%
6		dppp	HOAc/NaOAc	—	—	100%	70%
7		dppp	PhOH	45%	—	55%	73%
8		dppp	PhOH	87%	13%	—	67%

[a] All reactions were performed in toluene at 105 °C.

The alkene geometry of adducts **3** and **4** has been confirmed by comparison to the literature for these known compounds.[8,10] Irradiation of the vinyl proton in adduct **10** results in no NOE enhancement of the sulfonamide N−H signal, which is also consistent with (*Z*)-olefin geometry.[12] The geometry of the remaining examples is assigned by analogy. Furthermore, this geometry corresponds to the thermodynamically more stable one.[13] Thus, that a single geometric isomer was obtained in all cases is quite reasonable considering the reaction conditions should favor thermodynamic control.

The ability to redirect the regioselectivity of addition of a nucleophile from the classical β-addition mode to an α-addition mode by simply changing the "base" is quite remarkable. The high nucleophilicity of the phosphine relative to acid−base reactions presumably accounts for the effect. The generality of this new mode of reactivity remains to be established, but the illustrations herein already indicate it is a useful approach for the synthesis of dehydroamino acids. A typical experimental procedure follows: To a solution of phthalimide (74 mg, 0.5 mmol), triphenylphosphine (13 mg, 0.05 mmol), and sodium acetate (21 mg, 0.25 mmol) in 1 mL of toluene at 105 °C were added sequentially acetic acid (15 mg, 0.25 mmol) and ethyl phenylpropiolate (97 mg, 0.5 mmol). After 18 h, the cooled reaction mixture was directly chromatographed on silica gel (1:1 diethyl ether−hexanes) to yield 141 mg (82% yield) of phthalimide **3**.

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Supporting Information Available: Spectroscopic data for the compounds in this study (4 pages). See any current masthead page for ordering and Internet access instructions.

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