A Practical and Efficient Synthesis of α-Diazo Alkynyl Substituted Esters

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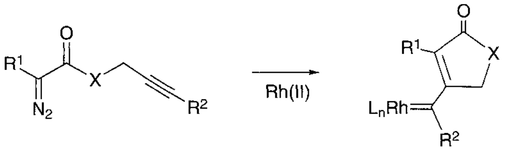
Received 28 August 1996

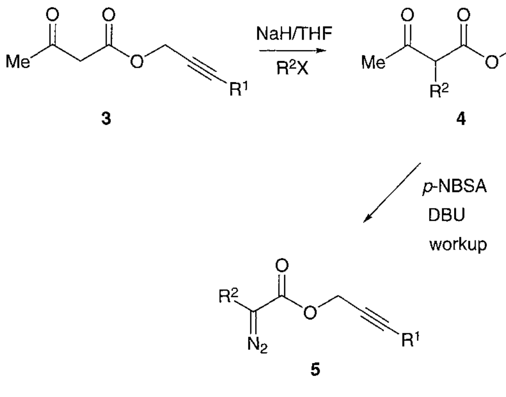
Abstract: An efficient method for the preparation of α-diazo alkynyl substituted esters is described. The key step involves diazo transfer of an α-alkyl substituted alkynyl β-keto ester with *p*-nitrobenzenesulfonyl azide and DBU.

α-Diazo carbonyl compounds are widely used in organic synthesis for preparing heterocyclic and carbocyclic rings.[1-10] The Arndt-Eistert sequence employs the Wolff rearrangement of an α-diazo ketone to a ketene in the one-carbon homologation of carboxylic acids.[11] Ring contraction of cyclic diazo ketones represents a general method for the preparation of highly strained small-ring compounds.[12] α-Diazo carbonyl compounds are also precursors to metallocarbenoid intermediates when exposed to many metal complexes or salts.[13] The high synthetic versatility of these compounds has brought diazo transfer reagents into wide usage as the most convenient method for achieving preparative diazotization.[14,15] The diazo transfer reaction proceeds best with azido sulfonyl compounds,[16] is quite general, but is limited by the requirement that the methylene hydrogens of the substrate be sufficiently acidic.[14]



1; X=CH$_2$; O 2; X=CH$_2$; O

Several years ago our group described a route for generating cycloalkenone carbenoids (*i.e.*, **2**) which involved the rhodium(II)-catalyzed decomposition of α-diazo alkynyl substituted carbonyl compounds.[17] In an effort to further extend these studies, we found it necessary to prepare a variety of diazo esters of type **1** (X=O). Despite the synthetic value of α-diazo esters, very few procedures for diazo transfer to the α-methylene of an ester have been developed. Formylation of esters does not lead to successful diazo transfer[18,19] although Taber has recently reported that benzoylation followed by reaction with *p*-nitrobenzenesulfonyl azide (*p*-NBSA) with DBU seems to work well in certain cases.[18] However, application of Taber's protocol to alkynyl substituted esters was totally unsuccessful resulting in very low yield (<10%) of the desired diazo esters. We now describe an alternative procedure for the preparation of α-diazo esters of type **1** which is based on the diazotization of α-substituted β-keto esters.



Alkylation of alkynyl substituted β-keto esters **3** proceeded in high yield by first treatment with NaH in THF followed by reaction with the appropriate alkyl halide. The diazo transfer works best when DBU and *p*-nitrobenzenesulfonyl azide is used.[16] Deacetylation readily occurred upon flash silica gel chromatographic workup and proceeded smoothly for each of the examples outlined in Table 1. This procedure makes α-diazo alkynyl as well as related unsaturated esters available as intermediates and opens the way for exploration of their rhodium(II)-catalyzed behavior.

The following procedure is representative. To a solution containing 3.0 g (22.7 mmol) of 3-phenylprop-2-yn-1-ol in 10 mL of xylene was added 3.0 mL (23.0 mmol) of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one[20] under N_2. After heating for 2 h at 140°C, the reaction was cooled to 25°C, filtered through celite and concentrated under reduced pressure. The crude β-keto ester was purified by flash chromatography to give 4.5 g (92%) of 3-oxobutyric acid 3-phenylprop-2-ynyl ester (**6**). To a suspension containing 95 mg (2.38 mmol) of 60% NaH in 10 mL of THF was added 0.44 g (2.03 mmol) of **6** dropwise. After stirring for 30 min at 25°C, 0.28 mL (2.35 mmol) of benzyl bromide was added in one portion. The reaction was stirred for 4 h at 60°C and then cooled to 25°C. The solution was poured into 50 mL of ice cold saturated NH_4Cl and then extracted with ether. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to give 3.59 g (91%) of 2-benzyl-3-oxobutyric acid 3-phenylprop-2-ynyl ester (**7**). To a dry 25 mL flask containing 0.27 g (0.88 mmol) of **7** was added 10 mL of dry CH_2Cl_2 and 0.30 g (1.32 mmol) of *p*-nitrobenzenesulphonyl azide. The flask was placed in an ice bath and 0.25 mL (1.67 mmol) of DBU was added dropwise. The mixture was stirred at 0°C for 10 min and filtered through a plug of silica. To this solution was added 2.2 mL (26 mmol) of pyrrolidine, and the mixture was stirred at 25°C for an additional 3 h. The solution was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 185 mg (72%) of 2-diazo-3-phenylpropionic acid 3-phenylprop-2-ynyl ester (**8**): IR (neat) 2086 and 1688 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 2H), 5.02 (s, 2H), 7.24-7.32 (m, 8H), and 7.44-7.47 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 29.4, 53.1, 83.1, 86.5, 122.1, 127.2, 128.3, 128.4, 128.8, 128.8, 131.9, and 137.0.

Acknowledgment: We gratefully acknowledge the National Science Foundation (CHE-9509496) for generous support of this work.

References and Notes

‡Recipient of a Graduate Fellowship from the Organic Chemistry Division of the American Chemical Society (1994-1995) sponsored by Proctor & Gamble, Co.

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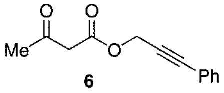
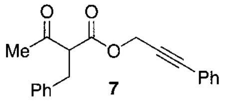
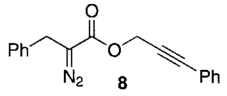
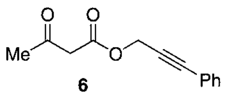
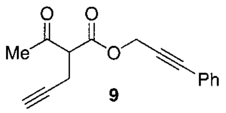
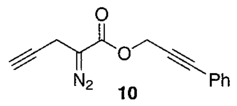
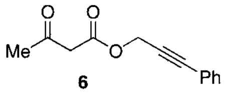
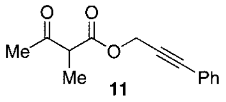
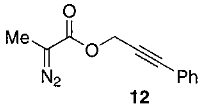
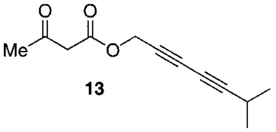
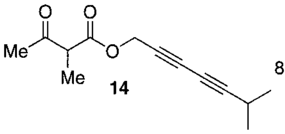
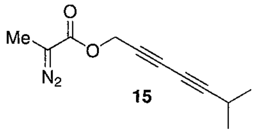
Table 1. Alkylation and Diazo Transfer

Ketoester	Alkylation Product	Yield(%)	Diazoester	Yield(%)
 **6**	 **7**	91	 **8**	72
 **6**	 **9**	73	 **10**	75
 **6**	 **11**	60	 **12**	81
 **13**	 **14**	82	 **15**	78

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