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Pauline Chiu^a & Sun TingWong^a

^a Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong Published online: 22 Aug 2006.

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A CONVENIENT PREPARATION OF (E)-3-PENTEN-2-ONE

Pauline Chiu,* Sun Ting Wong

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

ABSTRACT: A convenient large-scale synthesis of (E)-3-penten-2-one has been described based on the synthesis of the corresponding β , γ -unsaturated ketone and its subsequent base-catalyzed olefin isomerization.

Although (E)-3-penten-2-one 1 is a useful five-carbon synthon capable of normal or umpolung reactivity,¹ it is not readily available as a starting material. It is supplied commercially in 65% purity, a mixture unacceptable for use in synthesis. Many of its published syntheses are not convenient for large-scale preparations of 1.² A synthesis by House involved the reaction of the stabilized ylid 2 with acetaldehyde (eq. 1).³ However, the practical preparation of the ylid turned out to be rather cumbersome on a large scale.

$$Ph_{3}P=CHCOMe + MeCHO \xrightarrow{CH_{2}Cl_{2}} (eq. 1)$$
2 1

^{*} To whom correspondence should be addressed.



Nakagawa et al. recently reported a synthesis of 1 by the addition of trimmethylaluminum or dimethylaluminum chloride to crotonyl chloride, a procedure which was viable for scaling up (eq. 2).⁴ In our laboratory, we have synthesized 1 routinely on 10 g scales from inexpensive and readily available reagents based on the Barbier synthesis of β , γ -unsaturated ketones as reported by Conia et al.⁵ From these compounds, the authors suggested that α , β -unsaturated ketones can be prepared via the isomerization of the olefin, but this had not been realized experimentally. When we had need of 1 in large quantities for our natural product synthesis, we also noted that 4-penten-2-one was a precursor to 1 by simply bringing the olefin into conjugation. The isomerization was expected to favour the formation of the more stable (E)-stereoisomer rather than the (Z)stereoisomer. In fact, we found that a variety of acidic conditions (oxalic acid, BF₃ etherate in dichloromethane) induced smooth conjugation to yield (E)-3-penten-2one. However, catalytic DBU appeared to be the reagent of choice, because the subsequent isolation of 1 by distillation from the reaction mixture was aided by the presence of the base.⁴ In repeated experiments by this procedure, we found that this overall two-step route was a simple, and highly practical synthesis of 1, requiring only ambient temperatures, and does not necessitate the use of pyrophoric or sensitive reagents. A detailed procedure, with a slight modification in the synthesis of 4-penten-2-one, is as follows.



An oven-dried 500 mL two or three-neck round-bottom flask equipped with an efficient stir bar was fitted with a water-cooled condenser topped with a CaCl₂ drying tube, while another neck was fitted with an addition funnel. Zn/Ag couple (22.0 g, 0.336 at. g.)⁵ and acetonitrile (14.0 mL, 0.266 mol, distilled from CaH₂) were placed inside the flask, and were suspended in 45 mL dry ether and 5 mL dry THF. The addition funnel was charged with allyl bromide (30.0 mL, 0.347 mol), which was added dropwise to the reaction mixture to maintain a reflux. After completing addition, the reaction was stirred at 25°C for an additional 10 hours. The entire reaction flask was placed in an ice bath, and the thick reaction mixture was diluted with 50 mL of ether added via the addition funnel. The funnel was then charged with cold 2.0 M HCl (~60 mL) and the acid was added to the cold mixture dropwise with stirring until the solids were completely dissolved. The organic layer was separated. The aqueous layer was back-extracted with 5×40 mL portions of ether. The combined organics were washed with saturated Na₂CO₃ until neutral. The organic solution was dried over anhydrous MgSO4 and filtered.

To this ethereal solution was added DBU (4.0 mL, 26.7 mmol). This reaction mixture was directly distilled at normal pressure with a short Vigreux column to remove initially the volatiles, then to isolate 1 (head temperature 100-115°C) in 16.3 g, 73% yield (~95% purity by nmr). Repeated multigram scale runs have routinely produced yields of 70-75%, allowing large batches of 1 to be generated conveniently.

This procedure for the synthesis for (E)-3-penten-2-one 1 is a simple and practical method to obtain this useful five-carbon synthon. The use of this versatile synthon toward the synthesis of natural products will be reported in due course.

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