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IMPROVED HIGHLY EFFICIENT SYNTHESIS OF α,β-ACETYLENIC KETONES. NATURE OF THE INTERMEDIATE FROM THE REACTION OF LITHIUM ACETYLIDE WITH BORON TRIFLUORIDE ETHERATE

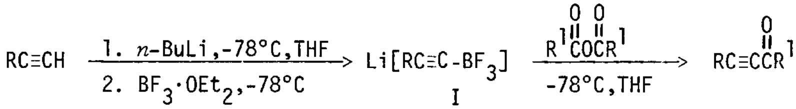
Herbert C. Brown*, Uday S. Racherla and Shankar M. Singh
Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907 USA

Abstract: A wide variety of α,β-acetylenic ketones were synthesized in very high yields *via* an exceptionally facile intermolecular reaction of lithium alkynyltrifluoroborates and carboxylic acid anhydrides.

α,β-Acetylenic carbonyl compounds are highly valuable precursors to a number of heterocyclic compounds,[1] C-nucleosides[2] and chiral pheromones.[3] The ability of α,β-acetylenic carbonyl compounds to readily undergo nucleophilic additions and cyclizations enhances the versatility of these substrates in organic synthesis.

Previously, asymmetric reductions of prochiral acetylenic ketones were reported[4,5] using Alpineborane™. For studies of this nature, we required a variety of α,β-acetylenic ketones which are structurally representative. In the past, a number of methods were reported for the synthesis of such α,β-acetylenic ketones.[6-11,22] While some methods suffer from poor overall yields, a few of the methods which give good yields employ relatively expensive palladium catalysts. Recently, Yamaguchi and coworkers reported a novel approach to the synthesis of such α,β-acetylenic ketones *via* the reaction of alkynylboron compounds[6,12] and tertiary amides. However, this procedure requires a three-fold excess of acetylene per mole of amide, a significant disadvantage. Therefore, as part of our continuing interest in the chemistry of alkynylboron compounds,[13-16] we decided to explore the reaction of alkynylborates with carboxylic acid anhydrides in the hope of achieving a simple and efficient synthesis of α,β-acetylenic ketones.

We were indeed gratified to find that lithium alkynyltrifluoroborates (I), readily obtained by the addition of $BF_3\cdot OEt_2$ to lithium acetylides at -78°C in THF, react smoothly with carboxylic acid anhydrides to provide α,β-acetylenic ketones (eq 1) in essentially quantitative yields.



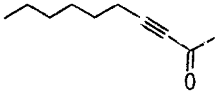
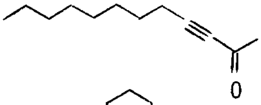
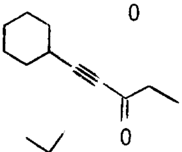
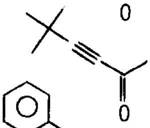
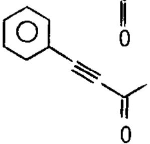
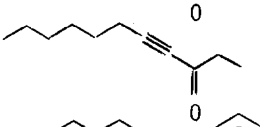
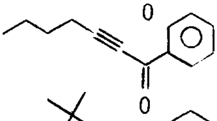
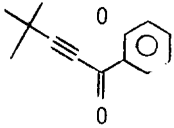
$$RC{\equiv}CH \xrightarrow[2.\ BF_3\cdot OEt_2,\,-78^\circ C]{1.\ n\text{-}BuLi,\,-78^\circ C,\,THF} \underset{I}{Li[RC{\equiv}C\text{-}BF_3]} \xrightarrow[-78^\circ C,\,THF]{R^1\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R^1} RC{\equiv}C\overset{O}{\overset{\|}{C}}R^1 \qquad (1)$$

Table I summarizes our results.

Yamaguchi and coworkers assumed that the reactive species obtained upon addition of $BF_3\cdot OEt_2$ to a lithium acetylide at -78°C in THF to be a trivalent boron compound, *viz.*, alkynyldifluoroborane[6,17] (II).

$$\underset{II}{RC{\equiv}C\text{—}BF_2}$$

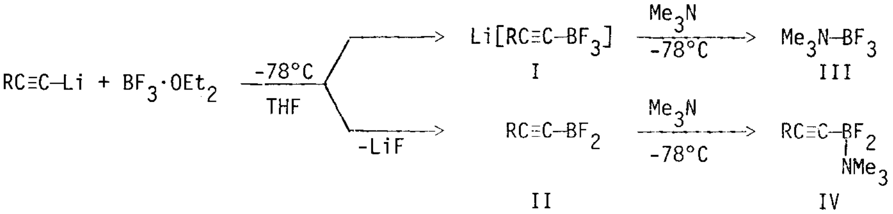
Table I. Synthesis of α,β-Acetylenic Ketones

Alkyne	Anhydride	α,β-Acetylenic Ketone[a,b]	b.p.	n^{20}_D	Yield (%)[c]
1-Octyne	Acetic		90°/0.3 mm [lit. 59-62°/0.5 mm][22a]	1.4440	72
1-Decyne	Acetic		122°/4 mm	1.4501	82
2-Cyclohexyl-1-ethyne	Propionic		78-80°/0.9 mm	1.4796	80
3,3-Dimethyl-1-butyne	Acetic		56°/15 mm [lit. 76°/56 mm][22c]	1.4319	71
2-Phenyl-1-ethyne	Acetic		76-77°/0.9 mm [lit. 89-91°/1 mm][22d]	1.5738	75
1-Octyne	Propionic		120°/15 mm	1.4472	74
1-Hexyne	Benzoic		110°/0.4 mm [lit. 110-114°/0.7 mm][22e]	1.5432	76
3,3-Dimethyl-1-butyne	Benzoic		91-92°/0.8 mm [lit. 125°/7 mm][22f]	1.5328	79

[a] All products gave satisfactory mass, IR, ^1H and ^{13}C NMR. [b] The chemical purity was in all cases ≥ 99%. [c] Isolated yields.

We undertook to verify their assumption by treating the boron intermediate with trimethylamine in the hope of forming the corresponding boron-amine adduct (Scheme 1).

Scheme 1

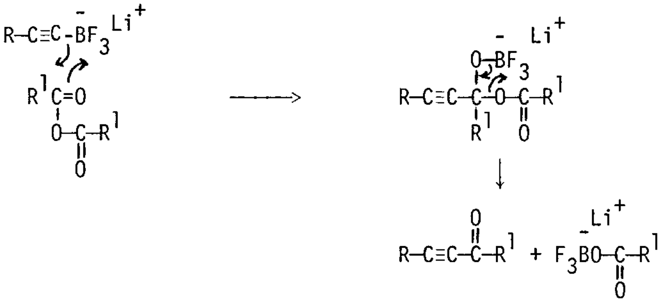


$$RC{\equiv}C{-}Li + BF_3{\cdot}OEt_2 \xrightarrow[THF]{-78°C} \begin{cases} Li[RC{\equiv}C{-}BF_3] \ (I) \xrightarrow[-78°C]{Me_3N} Me_3N{-}BF_3 \ (III) \\ \xrightarrow{-LiF} RC{\equiv}C{-}BF_2 \ (II) \xrightarrow[-78°C]{Me_3N} RC{\equiv}C{-}\underset{NMe_3}{BF_2} \ (IV) \end{cases}$$

The ^{11}B NMR spectrum of the reaction mixture obtained from the addition of $BF_3{\cdot}OEt_2$ to a THF solution of the lithium acetylide at -78°C showed a signal at δ -1.40 ± 0.06 (with respect to $BF_3{\cdot}OEt_2$ δ 0.0 as reference). On the basis of the ^{11}B chemical shift alone, it was difficult to decide whether this species was I or II. However, the addition of an equimolar amount of Me_3N at -78°C to the reaction mixture yielded a new species whose spectrum revealed the slow but complete conversion of the original peak at δ -1.40 $\pm$ 0.06 into a symmetrical quartet centered around δ 0.1, corresponding to $Me_3N{-}BF_3$[18] (III, Scheme 1). This suggested to us that the original species obtained from the addition of $BF_3{\cdot}OEt_2$ to a lithium acetylide must be I and not II. Had the species been II, we should have expected to observe a triplet in the ^{11}B NMR spectrum corresponding to the alkynyldifluoroborane-trimethylamine complex[18] (IV).

On the basis of the above evidence, we believe that the reactive species in the reaction with anhydrides (eq 1) is a lithium alkynyltrifluoroborate complex (I), which reacts with anhydrides according to the sequence shown below (Scheme 2).

Scheme 2



The following experimental procedure for the synthesis of 3-dodecyn-2-one is representative. To a solution of 1-decyne (4.15 g, 30 mmol) in THF (30 mL) at -78°C, *n*-butyllithium (19.5 mL, 1.54 *M*, 30 mmol) in hexane was slowly added, maintaining a nitrogen atmosphere. The reaction mixture was stirred for 1 h at -78°C and $BF_3{\cdot}OEt_2$ (4.26 g, 30 mmol) was added dropwise. Stirring was continued for 15 min and then acetic anhydride (4.59 g, 45 mmol) in THF (10 mL) precooled to -78°C was added all at a time.[19] The reaction was continued for 15 min at -78°C and aq NaOH (50 mL, 2 *N*) was added. The reaction mixture was warmed to room temperature and extracted with ether. The ethereal extract was liberally washed with brine, dried over anhydrous $MgSO_4$ and filtered. Evaporation of all volatiles, followed by distillation, afforded 3-dodecyn-2-one (4.43 g, 82% yield).

Carbon-carbon bond formation *via* the intramolecular reactions of organoborates are well documented in the literature.[20] However, few examples are now known which involve an intermolecular transfer reaction for organoborates.[21] The present synthesis of α,β-acetylenic ketones from alkynylborates and carboxylic acid anhydrides offers a rare example of a reaction of the latter type. We are currently exploring the full scope of this useful reaction.

ACKNOWLEDGEMENT

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$$\mathrm{Li[RC{\equiv}C)_4B]}$$

IV

Indeed, lithium tetraoctynylborate (IV), synthesized by treating 4 equiv of lithium acetylide with one of $BF_3 \cdot OEt_2$ in THF at 0°C, exhibits a ^{11}B chemical shift at the same place and does not react with anhydrides at -78°C.
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