1,3-Dienes from ketones *via* the Shapiro reaction

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This paper is dedicated to Professor Otto Meth-Cohn to mark his 65th birthday and to acknowledge his many contributions to synthetic and heterocyclic chemistry

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Abstract

1,3-Dienesare prepared from ketones by an efficient two step procedure. Ketone-derived trisylhydrazones are subjected to an organolithium-induced Shapiro reaction to produce the corresponding vinyllithium species. Transmetallation to organocopper intermediates then allows efficient dimerisation to a range of alkyl substituted 1,3-dienes. Some limitations of the procedure are also described.

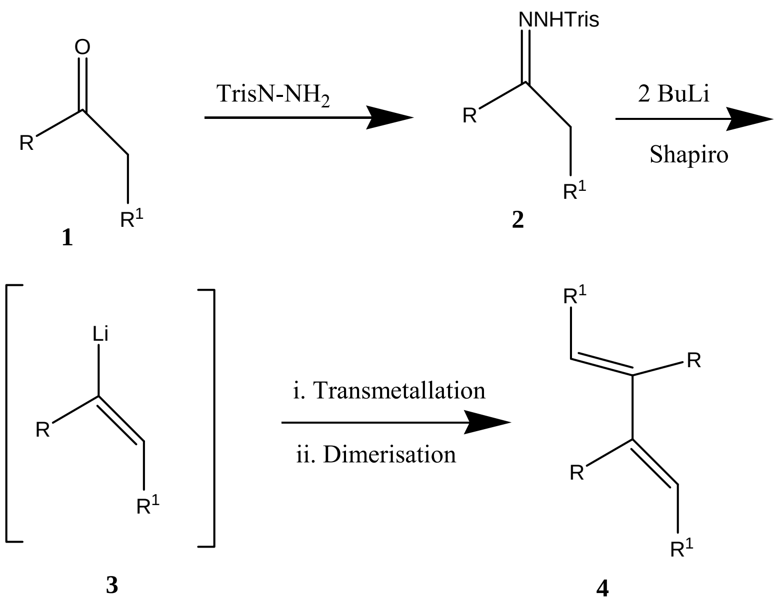
Keywords: 1,3-Dienes, Shapiro reaction, vinyllithium reagents, vinylcopper reagents, dimerisation

Introduction

1,3-Dienes are important synthetic intermediates, finding particular application in the Diels-Alder reaction.[1] We have a long-standing interest in the preparation of conjugated polyenes[2,3] and recently reported a convenient entry to 1,4-disubstituted buta-1,3-dienes *via* the palladium(II)-mediated homocoupling of organostannanes.[4] In seeking to convert ketones 1 into 2,3-disubstituted- and more highly substituted butadienes 4, we envisaged a new extension of the Shapiro reaction[5] (Scheme).

Thus, conversion of the ketones 1 into the corresponding sulfonylhydrazones 2 followed by the organolithium-induced Shapiro reaction is known to produce vinyllithium intermediates 3.[5]We planned to transmetallate 3 to produce a vinyl organometallic species which would undergo dimerisation to give dienes 4.

Tris = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$SO$_2$-)



Scheme 1

Results and Discussion

Initial studies were carried out with tosylhydrazones but it was soon established that better results were obtained using 2,4,6-triisopropylbenzenesulfonyl (trisyl) hydrazones.[5b] The trisylhydrazones 2a-h were readily prepared, most in almost quantitative yield (Table), simply by stirring a THF solution of the appropriate ketone and trisylhydrazide and then removing the solvent *in vacuo* following the procedure reported by Bertz and Dabbagh.[6]

Treatment of a THF solution of the trisylhydrazones 2 with 2.1 equivalents of *n*-butyllithium at -78 ˚C gave deep orange coloured solutions. Upon warming to 0 ˚C for a few minutes, the evolution of nitrogen gas was evident leaving a yellow solution of vinyllithium species 3. This solution was then recooled to -78 ˚C. Preliminary investigations into the transmetallation-dimerisation were carried out with $MnCl_2$, $Ti(O^iPr)_3Cl$ and $PhI(OAc)_2$ giving no observable diene upon workup, although a combination of $Pd(MeCN)_2Cl_2$ and $CuCl_2$ produced 4a in low yield (43%).It is known that vinyllithium reagents undergo transmetallation to organocopper species and that these can undergo oxidative coupling to produce 1,3-dienes.[7]A range[8] of copper(I) salts were therefore employed to effect the dimerisation of the vinyllithium reagent derived from trisylhydrazone 2a (Table, entry i). The use of copper(I) iodide gave good yields for the formation of 4a (66-78%) but was not general. The optimum procedure, and the one which appeared the most general, involved the use of one equivalent of $(CuI.PBu_3)_4$[7a] in THF at -78 ˚C followed by warming to room temperature and stirring at this temperature for 18 hours. The efficiency of $(CuI.PBu_3)_4$ compared to other Cu(I) salts may well be due to its high solubility in THF. The optimised procedure produced diene 4a in 68% yield; no other products were observed indicating regioselective deprotonation at the methyl group as was anticipated.[5] Diene 4a has been used to prepare protein kinase C inhibitors: this synthesis from nonanone (68% over 2 steps) compares favourably with the published route from nonanoic acid (6 steps, *ca.* 10%).[3] Addition of 1% triethylamine to column chromatography eluents was found to be necessary to avoid double bond isomerisation, but when pure the dienes could be stored under a nitrogen atmosphere in the freezer for a number of months.

Two other 2,3-disubstituted butadienes were also prepared using this methodology (Table, entries ii and iv). In the case of cyclohexyl methyl ketone trisylhydrazone 2b, selective deprotonation of the methyl group occurred giving diene 4b in good yield. Cyclohexyl ethyl ketone trisylhydrazone 2c did not produce any diene 4c, however, apparently failing to undergo the Shapiro reaction and demonstrating a limitation of this methodology (Table, entry iii). In the case of acetophenone trisylhydrazone 2d vinyllithium formation appeared to proceed normally but the coupling was sluggish (Table entry iv). In this example the reaction was heated to reflux for 18 hours after the addition of the copper complex: this produced 4d in 23% yield (no diene was obtained under the standard conditions). It seems likely that this low yield reflects the thermal stability of the intermediate organocopper species.

Next, we investigated the use of cyclic ketones ultimately producing 1,2,3,4-tetrasubstituted butadienes (Table entries v and vi). Efficient deprotonation of the hydrazones 2e-i could only be achieved by using a THF-TMEDA (9:1) solvent mixture in the Shapiro reaction,[5b] but the standard transmetallation-dimerisation conditions afforded dienes 4f and 4g in satisfactory yield. No dienes were isolated from the reaction of cyclopentanone trisylhydrazone 2e but the low stability of cyclopentenyllithium prepared in this way has been noted previously.[9] In the case of cyclododecanone trisylhydrazone 2h, no diene was obtained but a 53% yield of cyclododecene was isolated, presumably indicating that the dimerisation may be precluded for steric reasons. Finally, the substituted cyclohexanone trisylhydrazone 2i, underwent efficient transformation to give diene 4i.

In summary, an efficient two-step procedure for the preparation of substituted buta-1,3-dienes from ketones has been developed and information on the scope and limitations of the methodology has been established.

Table 1. Yields of hydrazones 2 and dienes 4

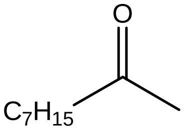
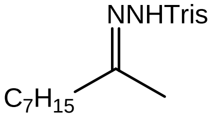
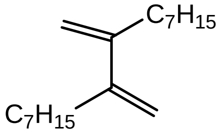
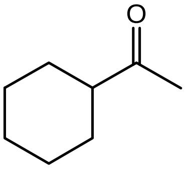
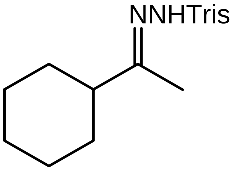
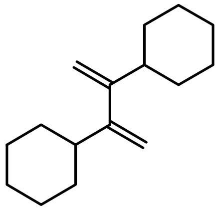
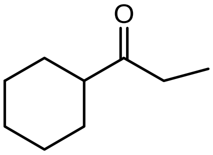
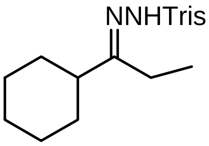
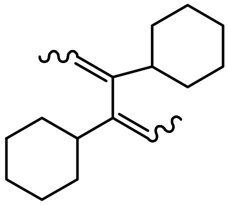
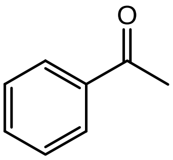
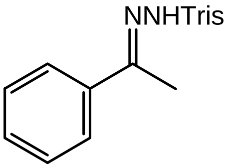
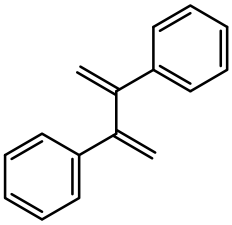
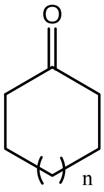
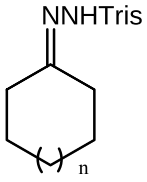
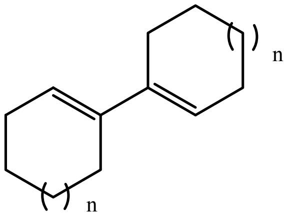
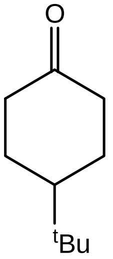
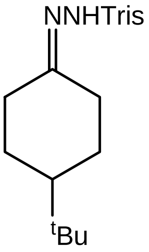
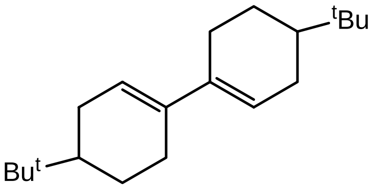
	Ketone	Hydrazone (Isolated yield)	Diene (Isolated yield)[a]
i	 1a	 2a (100%)	 4a (68%)[b]
ii	 1b	 2b (100%)	 b (69%)
iii	 1c	 2c (77%)	 4c (-)[c,d]
iv[e]	 1d	 2d (81%)	 4d (23%)
v[d]	 1e, n = 0 f, n = 1 1g, n = 2 1h, n = 7	 2e, n = 0 (99%) 2f, n = 1 (100%) 2g, n = 2 (100%) 2h, n = 7 (91%)	 4e, n = 0 (-)[c] 4f, n = 1 (65%) 4g, n = 2 (52%) 4h, n = 7 (-)[f]

Table 1. Continued

vi[d]	 1i	 2i (97%)	 4i (65%)

[a] Unless otherwise stated, *n*-BuLi in THF at -78 ˚C was used for deprotonation. (CuI.$PBu_3)_4$was added at -78 ˚C followed by warming to room temperature and stirring at this temperature for 18 hours.

[b] A 12% yield of a 1:1 mixture of 4a and 1-nonene was obtained with nonan-2-one tosylhydrazone, using CuI for the transmetallation. Using 2a and CuI, 4a was obtained in 66-78% yield.

[c] None of the expected product was observed with only unidentified polar by-products being obtained.

[d] THF-TMEDA (9:1) was used as solvent for the second step.

[e] Coupling reaction heated to reflux for 18 h (no diene was obtained under standard conditions).

[f] Cyclododecene (53%) was obtained.

Experimental Section

Compounds 2b-i and 4a,b,d,f,g,i are known andgave data consistent with those published.

Representative Procedures

(a) Nonan-2-one trisylhydrazone (2a)

To a stirred solution of trisylhydrazide (1.49 g, 5 mmol) in THF (35 mL) was added nonan-2-one (0.85 mL, 5 mmol). After 3 h, the solvent was removed *in vacuo* and the residue dried at 1 mm Hg to give nonan-2-one trisylhydrazone 2a (2.13 g, 100%) as a colourless solid, mp 86 - 88 ˚C dec.; R_f 0.42 (light petroleum - diethyl ether, 1:1); IR (Nujol®, cm^{-1}) 3242 (NH), 1599, 1562, 1379, 1328, 1167; δ_H (270 MHz, $CDCl_3$) 7.16 (2 H, s, aromatic), 4.22 (2 H, sept., *J* 7 Hz, 2 x C<u>H</u>Me₂), 2.90 (1 H, sept., *J* 7 Hz, C<u>H</u>Me₂), 2.17 (2 H, t, *J* 7 Hz, CH_2), 1.90 + 1.77 (3 H, 2 x s, CH_3), 1.45 - 1.15 (28 H, m, 5 x CH_2 + 6 x isopropyl CH_3), 0.85 (3 H, br. t, CH_3); δ_C

(67.9 MHz, $CDCl_3$) 157.0 (C), 153.0 (C), 151.3 (2 x C), 131.4 (C), 123.6 (2 x CH), 38.6 (CH_2), 34.1 (CH), 31.6 (CH_2), 29.9 (2 x CH), 28.8 (CH_2), 28.7 (CH_2), 25.8 (CH_2), 24.7 (4 x CH_3), 23.5 (2 x CH_3), 22.5 (CH_2), 15.2 (CH_3), 14.0 (CH_3); MS (CI) *m/z* 423 (MH^+, 100%), 281 (8), 251 (12), 157 (15) [HRMS (CI) 423.3050. $C_{24}H_{43}N_2O_2S$ requires 423.3045 (1.1 ppm error)].

(b) 2,3-Diheptylbuta-1,3-diene(4a)

To a stirred solution of hydrazone 2a (0.422 g, 1 mmol) in dry THF (5 mL) at -78 ˚C was added *n*-butyllithium (2.5 M solution in hexanes, 0.84 mL, 2.1 mmol) to give an orange solution. After stirring for 30 min, the reaction was warmed to 0 ˚C for 5-10 min until nitrogen evolution had ceased. The yellow solution was then re-cooled to -78 ˚C and added *via* cannula to a solution of $(CuI.PBu_3)_4$ (1.571 g, 1 mmol) in dry THF (5 mL) at -78 ˚C. After 30 min, the reaction was warmed to rt and stirred for 18 h. The black reaction mixture was poured into satd. NH_4Cl - conc. NH_3 solution (4:1) (25 mL) and diethyl ether (25 mL) and then filtered through Celite® into a separating funnel. After separation, the organic phase was washed with satd. $NaHCO_3$ solution (2 x 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (petroleum ether-Et_3N, 99:1) to give 2,3-diheptylbuta-1,3-diene(4a) as a clear, colourless oil (0.085 g, 68%), R_f 0.56 (light petroleum);with spectroscopic data consistent with those published.[3,10]

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