Acc. Chem. Res. **1983**, *16*, 55-59

Recent Applications of the Shapiro Reaction

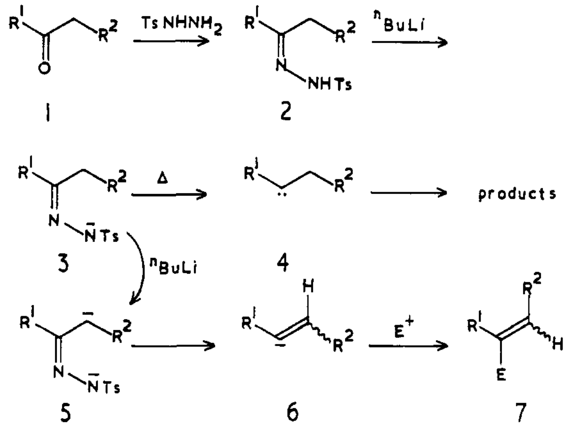
ROBERT M. ADLINGTON and ANTHONY G. M. BARRETT*

Department of Chemistry, Imperial College of Science & Technology, London SW7 2AY, United Kingdom

Received April 30, 1982 (Revised Manuscript Received September 27, 1982)

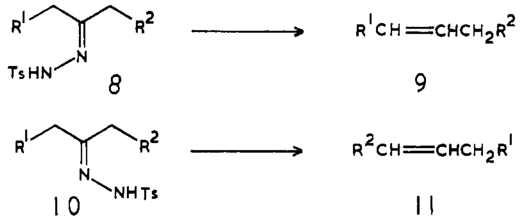
In 1898 Curtius and Lorenzen reported that benzenesulfonyl chloride reacted with hydrazine to give (phenylsulfonyl)hydrazine.[1] As expected, this condensed cleanly with benzaldehyde or acetone, forming the crystalline (phenylsulfonyl)hydrazone derivatives. These early workers noted both the acidity of these substances, associated with the N-H proton adjacent to the electron-withdrawing phenylsulfonyl group, and their instability. Decomposition by heating gave the readily expelled benzenesulfinic acid and nitrogen. Bamford and Stevens, 54 years later, first applied these observations in a useful synthetic procedure.[2] Subsequently, in 1967, ketone (4-tolylsulfonyl)hydrazones were used as precusors for the synthesis of vinyllithium reagents.[3] The Shapiro reaction was born.

Ketones (1) condense readily with (4-tolylsulfonyl)hydrazine to give the invariably crystalline (4-tolylsulfonyl)hydrazones (tosylhydrazones) (2). These derivatives contain an array of acidic functionality. Thus, reaction with sodium hydride or methoxide or *n*-butyllithium gives the N-monoanion **3**. Anion **3** contains two good leaving groups: the 4-toluenesulfinate anion and nitrogen. Thus, on warming up to 150–200 °C, **3** decomposes, giving the carbene **4**, which undergoes, for example, bond insertion reactions. This tosylhydrazone (**2**) to carbene (**4**) transformation is termed the aprotic Bamford–Stevens reaction.[2]



Alternatively, the monoanion **3** may be further metalated with *n*-BuLi to give the C,N-dianion **5**. This intermediate (**5**) still contains the same two good leaving groups, and it readily decomposes at 0–25 °C, giving the vinyl carbanion **6**. Intermediate **6** is then available for interception with an electrophile (E^+) to give the product alkene **7**. Since, in principle, the electrophile can be easily varied, the range of alkenes **7** available is diverse. In its simplest form, **6** is quenched by water ($E^+ = H_2O$) to give **7** (E = H). This preparation of unfunctionalized alkenes (**7**) (E = H) from ketone tosylhydrazones (**2**) is termed the Shapiro reaction.[3] In this case it is often advantageous to use lithium diisopropylamide as the base to generate the dianion (**5**).

With an unsymmetrical ketone, the question of regioselectivity arises. In principle, there are two possible regioisomeric alkene products providing that both flanks of the tosylhydrazone C=N possess acidic C–H protons. In practice, regioselectivity depends on the geometry of the initial tosylhydrazone and on the choice of solvent. In hydrocarbon or ether solvents the dianion **5** formed is exclusively syn.[4] This syn-dianion effect[3,5] probably results from kinetic-controlled deprotonation: the nitrogen-centered anion directs the *n*-BuLi to remove the nearest C–H proton. Thus, in these solvents the regioselectivity is controlled solely by the tosylhydrazone geometry; isomers **8** and **10** give respectively **9** and **11** exclusively. In strongly cation coordinating solvents, e.g., *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), the directional influence of the nitrogen center is overwhelmed and the least-substituted vinyl carbanion is produced.[6]



The Shapiro reaction thus permits the convenient conversion of a ketone into a single substituted olefin. Both olefins and ketones are fundamental building blocks in synthetic organic chemistry; both may be readily and easily transformed into an array of diverse functionality. Thus, reactions that interconvert ketones and olefins are of vital importance. This account will highlight the versatility of the Shapiro reaction in synthetic organic chemistry.

The Shapiro Reaction Exemplified

Until 1975, the Shapiro reaction was utilized principally[3] for the preparation of simple alkenes (**7**, E = H, D). This resulted from two severe preparative shortcomings. The fragmentation of **5** to **6** is so slow

Robert M. Adlington received his B.Sc. (1977) and Ph.D. (1980) from Imperial College of Science and Technology, University of London. He is currently a member of Jack E. Baldwin's research team at Oxford University.

Anthony G.M. Barrett obtained his B.Sc. (1973) and Ph.D. (1975) at Imperial College, under Sir Derek Barton's guidance. In 1975 he became a faculty member at Imperial. His current research interests are the development of new synthetic methods and the total synthesis of several natural products.

---

(1) T. Curtius and F. Lorenzen, *J. Prakt. Chem.*, **58**, 160 (1898).

(2) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(3) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967); R. H. Shapiro, *Org. React.* (*N.Y.*), **23**, 405 (1975).

(4) R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuano, *Tetrahedron Lett.*, 1811 (1975).

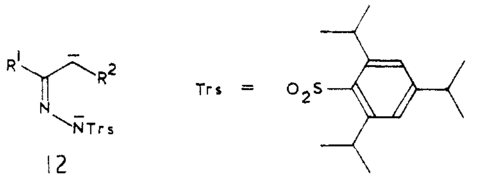
(5) The syn-dianion effect breaks down for α,β-unsaturated ketones: W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.*, **99**, 3414 (1977).

(6) A. R. Chamberlin, J. E. Stemke, and F. T. Bond, *J. Org. Chem.*, **43**, 147 (1978).

0001-4842/83/0116-0055$01.50/0

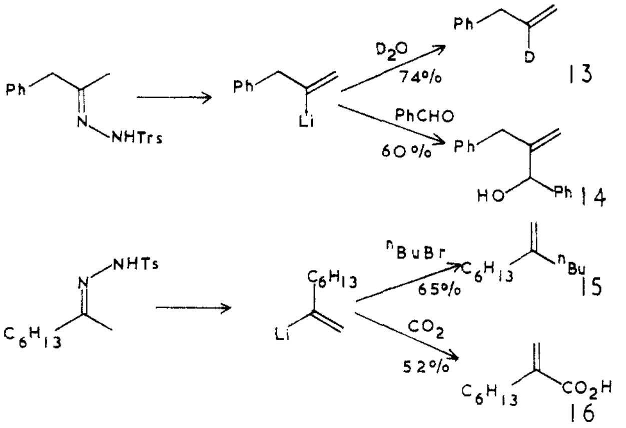
that partial protonation of **6** by the solvent takes place on the same time scale.[4] Thus, although this makes little difference to the yield of the alkene (**7**, E = H), it is catastrophic for any other product (**7**, E ≠ H). Second, the 4-tolylsulfonyl ring is partially ortho-metalated by the *n*-BuLi.[6] Thus **7** (E ≠ H) are generally produced in low yield, admixed with byproducts.

Fortunately, the preparative disadvantages have been overcome and the Shapiro reaction has been generalized. Both ketone (phenyl- and 4-tolylsulfonyl-) hydrazones (**2**) have been converted in good yield into the vinyl carbanions **6** by using excess *n*-BuLi in TMEDA.[7] This reagent cocktail is crucial in that the rate of fragmentation of **5** giving **6** is rapid, **6** is not competitively protonated by the solvent, and the excess *n*-BuLi compensates for competitive ortho-metalation in the aromatic ring. Second, Bond[6] introduced ketone (2,4,6-triisopropylphenylsulfonyl)hydrazones (trisylhydrazones). These substances are converted in high yield into **6**. Orthometalation is impossible, and **12**

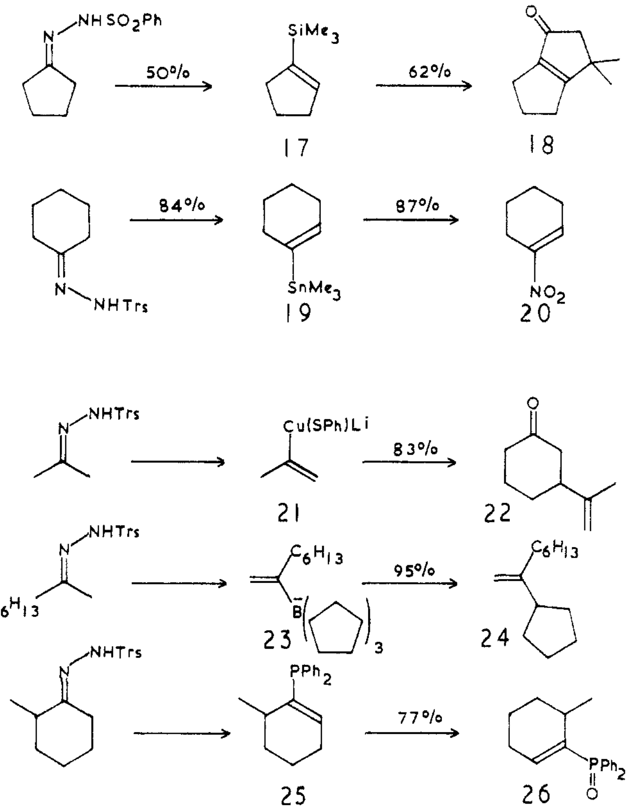


fragments very rapidly to **6** at 0 °C in hexane–TMEDA (9:1) as solvent. The Bond modification is especialy elegant since metalation is stoichiometric and, thus, large excesses of base and electrophile are avoided.

In the wake of these improvements, the synthetic uses for the Shapiro reaction are indeed legion. For example, phenylacetone and 2-octanone have been converted into 3-phenyl-2-lithiopropene and 2-lithiooctene. When D_2O, benzaldehyde, 1-bromobutane, and carbon dioxide were used as electrophiles, **13**, **14**, **15**, and **16** were readily obtained.[6,8] Alkenyllithium intermediates are



powerful nucleophiles, and condensation with some electrophiles may be uncontrollable. The reactivity of the vinyl anion intermediates in the Shapiro reaction have been moderated by reaction with Me_3SiCl, Me_3SnCl, PhSCu, Ph_2PCl, and tricyclopentylborane, giving, for example, **17**, **19**, **21**, **23**, and **25**. These alkene derivatives are themselves useful synthetic intermediates. The powerful electrophiles 3-methyl-2-butenoyl chloride[9] and tetranitromethane[10] readily and cleanly condensed respectively with **17** and **19**, giving the bicyclic ketone **18** and nitroolefin **20**. The cuprate



reagent **21** and 2-cyclohexenone gave **22**[11] where the presence of copper ensured exclusive 1,4-addition to the enone. With iodine, the ate complex **23** was oxidized, giving **24**.[12] This was formed via cyclopentyl group migration. Finally, the oxidation of **25** using hydrogen peroxide gave **26**.[13]

The conversion of simple ketones into heavily functionalized alkenes is preparatively simple. Products including **13**–**26** are useful intermediates for further synthetic transformations. Clearly, the Shapiro reaction is indeed versatile.

Carbonyl Transposition

Since ketone chemistry is fundamental to functional group interconversions, the 1,2-carbonyl transposition reaction is of special merit. The Shapiro reaction has been utilized principally[14] in two ways to mediate such a molecular change. Paquette[15] has widely applied vinylsilanes as key intermediates. For example, **27** was converted into **29** via **28**. On reaction with 3-chloroperoxybenzoic acid, **29** gave the derived epoxide. Sequential ring opening with lithium aluminum hydride and acidic sodium dichromate oxidation gave the transposed ketone **30**. Clearly **30** was formed via desilyation under the acidic oxidation conditions.

---

(7) J. E. Stemke and F. T. Bond, *Tetrahedron Lett.*, 1815 (1975).

(8) J. E. Stemke, A. R. Chamberlin, and F. T. Bond, *Tetrahedron Lett.*, 2947 (1976).

(9) L. A. Paquette, W. E. Fristad, D. S. Dime, and T. R. Bailey, *J. Org. Chem.*, **45**, 3017 (1980).

(10) E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, **21** 1113 (1980).

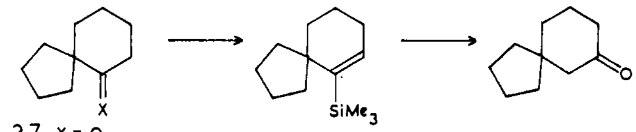
(11) A. S. Kende and L. N. Jungheim, *Tetrahedron Lett.*, **21**, 3849 (1980).

(12) K. Avasthi, T. Baba, and A. Suzuki, *Tetrahedron Lett.*, **21**, 945 (1980).

(13) D. G. Mislankar, B. Mugrage, and S. D. Darling, *Tetrahedron Lett.*, **22**, 4619 (1981).

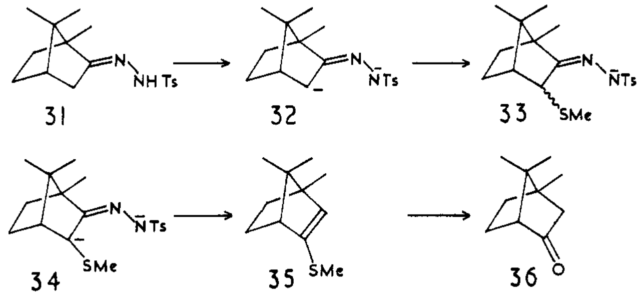
(14) The use of the Shapiro reaction in carbonyl transposition was introduced by Reusch, albeit in a lengthy sequence of transformations: K. M. Patel and W. Reusch, *Synth. Commun.*, **5**, 27 (1975).

(15) W. E. Fristad, T. R. Bailey and L. A. Paquette, *J. Org. Chem.*, **45**, 3028 (1980).

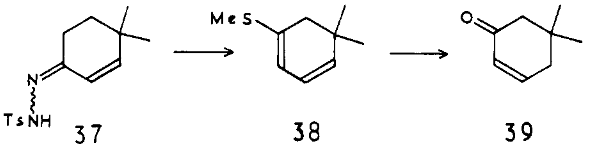


27 X = O
28 X = NNHSO$_2$Ph
29
30

Two Japanese groups[16] have utilized the alkanesulfenylation of anion **5** as a concise method for 1,2-carbonyl transposition. For example, **31** was metalated by *n*-BuLi in TMEDA-THF at -50 to -30 °C to give **32**, which was quenched with dimethyl disulfide to give **33**. Without quenching, this was remetalated with *n*-BuLi and the resulting dianion **34** allowed to fragment at room temperature. Aqueous workup gave **35** (45%). On hydrolysis ($HgCl_2$, MeCN, H_2O), **35** gave the transposed ketone **36** (84%). This convenient reaction has been extended to 1,2-enone transposition. For example, enone derivative **37** was transposed into **39** (51%) via the dienyl sulfide **38**. The success of the reaction that converted **31** into **36** and **37** into **39** depended upon suppression of the rate of fragmentation of **5** at low temperature, thus permitting its capture by an electrophile (MeSSMe).



31 **32** **33** **34** **35** **36**



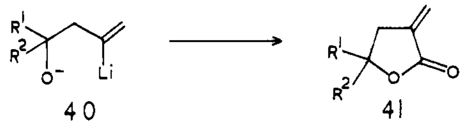
37 **38** **39**

Polyfunctional Precursors and the Shapiro Reaction

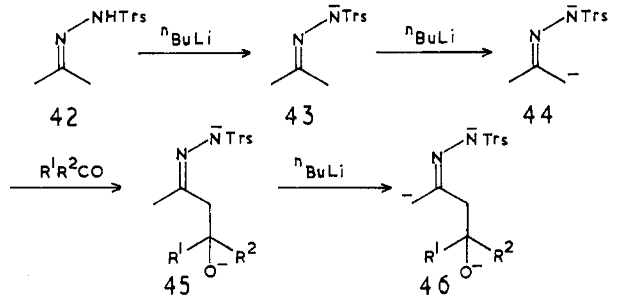
With few exceptions[17] the conversion of ketone (arylsulfonyl)hydrazones into vinyl carbanions has largely been applied to simple systems. Presumably the anticipation of chemoselectivity problems in polyfunctional molecules has dictated against using the Shapiro reaction. However, since this ketone-to-olefin conversion is so flexible, we sought its application to more functionalized molecules.

3-Methylenetetrahydro-2-furanone Synthesis

The 3-methylenetetrahydro-2-furanone **41** is notable for its natural occurrence in diverse sesquiterpene lactones including vernolepin. Several of these Michael acceptors exhibit cytotoxicity and have thus been subjected to extensive synthetic investigations. We considered that derivatives of these α-methylene lactones **41** should be available simply by the carboxylation of the dianion **40** and subsequent acidification. Clearly, **40** should be available by using the Shapiro reaction. Thus, metalation of a β-hydroxy trisylhydrazone should provide **40** directly after loss of the arenesulfinate anion and nitrogen.

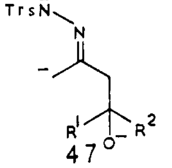


40 **41**

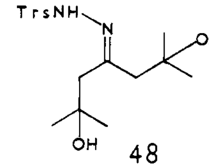


42 **43** **44** **45** **46**

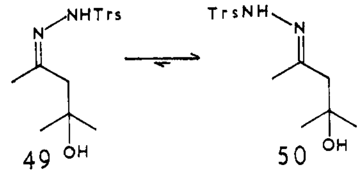
Acetone trisylhydrazone (**42**) reacted cleanly with *n*-BuLi in 1,2-dimethoxyethane (DME) solution at -78 °C to give dianion **44** as a beautiful golden yellow solution. Indeed, this metalation is self-indicating[18] since the intermediate monoanion **43** is colorless and its complete formation is confirmed by a yellow end point. The golden solution could be titrated at -78 to -50 °C with an aldehyde or ketone to a colorless end point, giving dianion **45**. Further metalation with *n*-BuLi in situ gave the trianion **46**, not **47**, as a bright orange solution. The formation of **46** ($R^1 = R^2 =$ Me) was readily confirmed by quenching with acetone or water to give **48** (31%) or **49** (95%), respectively.[19] Isomerization of **49** took place on standing, giving the more stable **50**. In the formation of **46**, the third deprotonation was anti to the arylsulfonyl group. Presumably, this resulted from suppression of syn-CH acidity by the adjacent oxyanion.[19,20]



47



48



49 **50**

The orange trianion (**46**) was unstable at 0 °C and, on warming from -78 °C, the color faded to pale yellow and nitrogen evolution took place. This self-indicating reaction gave the oxy vinyl dianion **40**. Carboxylation at -78 °C and acidification with trifluoroacetic acid gave the α-methylenebutyrolactones **41** in 33-66% overall yield. Clearly our "one pot" reaction provides a con-

---

(16) T. Nakani and T. Mimura, *Tetrahedron Lett.*, 531 (1979); T. Mimura and T. Nakai, *Chem. Lett.*, 931 (1980), 1099 (1980), 1579 (1981); S. Kano, T. Yokomatsu, T. Ono, S. Hibino, and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 414 (1978).

(17) For example see P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, **42**, 1717 (1977); C. A. Bunnell and P. L. Fuchs, *J. Am. Chem. Soc.*, **99**, 5184 (1977); B. Cazes, E. Guittet, S. Julia, and O. Ruel, *J. Organometal. Chem.*, **177**, 67 (1979); A. S. Kende and J. P. Rizzi, *J. Am. Chem. Soc.*, **103**, 4247 (1981); P. A. Grieco, T. Oguri, and S. Gilman, *ibid.*, **102**, 5886 (1980); W. Oppolzer, and R. L. Snowden, *Tetrahedron Lett.*, 3505 (1978).

(18) M. F. Lipton, C. M. Sorensen, A. C. Sadler, and R. H. Shapiro, *J. Organometal. Chem.*, **186**, 155 (1980).

(19) R. M. Adlington and A. G. M. Barrett, *J. Chem. Soc., Perkin Trans.* 1, 2848 (1981).

(20) M. F. Lipton and R. H. Shapiro, *J. Org. Chem.*, **43**, 1409 (1978).

$$42 \xrightarrow{^{n}\mathrm{BuLi}} 44 \xrightarrow{R^1R^2CO} 45 \xrightarrow{^{n}\mathrm{BuLi}}$$

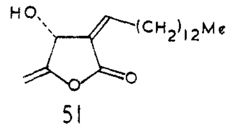
$$46 \xrightarrow{0\,°C} 40 \xrightarrow[CF_3CO_2H]{CO_2;} 41$$

venient entry to these useful molecules (41). The reaction is aesthetically pleasing to carry out, being self-indicating at each stage.[19,21]

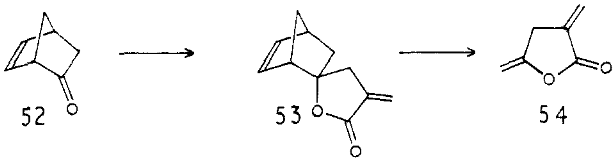
The first step in the synthesis of **41** is a masked aldol condensation (**44** → **45**). Thus the lactones **41** were alternatively available from β-hydroxy ketones. 4-Hydroxy-4-methyl-2-pentanone reacted smoothly and without β elimination with trisylhydrazine in dichloromethane to give **49** and **50** (1:2, 93%). The two isomers could be readily separated and metalated with *n*-BuLi in DME at −78 °C to give the trianions **46** and **47** ($R^1 = R^2 =$ Me), respectively, as orange and golden yellow solutions. Warm up to −3 °C, carboxylation at −78 °C, and acidification gave the same α-methylene lactone (**41**, $R^1 = R^2 =$ Me) in 78 and 49% yield, respectively.

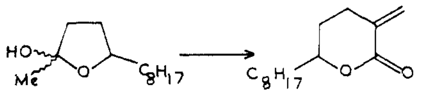
3,5-Dimethylenetetrahydro-2-furanone (54)

Lactone **54** is the parent heterocycle for several naturally occurring substances including obtsusilactone A (**51**). In principle, **54** should be available by condensing **44** with a ketene equivalent. Thus, **44** was reacted with 5-norbornen-2-one (**52**) in the usual way. Further metalation, fragmentation to the vinyl anion, carboxylation, and acidification with acetic acid gave the spiro lactone **53** (61%). Flash vacuum pyrolysis (FVP) of **53** at 550 °C and 10^{-4} mm gave **54** (83%) formed via a retro-Diels–Alder process.[22]



51



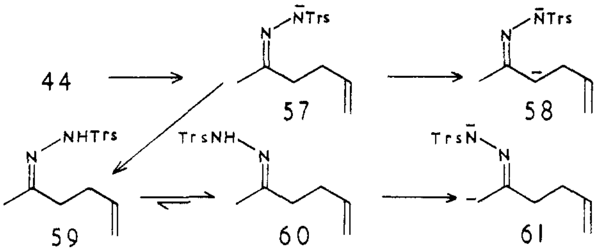


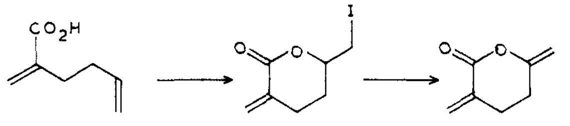
55 56

3-Methylenetetrahydro-2-pyranone Synthesis

Although the β-hydroxytrisylhydrazones **49** and **50** could be readily converted into the lactone **41** ($R^1 = R^2$ = Me), the reaction was less successful for γ-hydroxy trisylhydrazones. We hoped that these compounds would readily provide the biologically important 3-methylenetetrahydro-2-pyranone derivatives. 5-Hydroxy-2-tridecanone (**55**) was reacted in sequence with trisylhydrazine, *n*-BuLi, carbon dioxide, and trifluoroacetic acid in the usual way to give lactone **56**, but in poor yield (23%). This unsatisfactory outcome resulted from instability of the intermediate trisylhydrazone.

As an alternative route to lactones related to **56**, we sought to use the allylation of the golden dianion **44**. In DME at −60 °C, allyl bromide reacted smoothly with **44** with discharge of color to give the geometrically stable anion **57**. Further metalation of **57** with *n*-BuLi gave the syn dianion **58**. **57** was protonated with acetic acid to allow metalation on the methyl group. The initial product **59** readily equilibrated with **60** (15:85, 94%). When this was metalated with *n*-BuLi, the *major* golden dianion formed was **61**. The opportunity to selectively prepare **58** or **61** underscores the excellence of the syn-dilithio effect.[19,22] Decomposition of **61** at −3 °C, carboxylation at −78 °C, and acidication gave the dienoic acid **62**. Without purification, this was iodolactonized ($NaHCO_3$, KI, I_2) to give the α-methylene lactone **63** in in 50% overall yield. On reaction with DBU in benzene at 70 °C, **63** gave the 3,6-dimethylene lactone **64** (64%). Without doubt, dianion **44** allylation provides a concise entry to functionalized unsaturated lactones. Elsewhere, Bond has reported the synthetic versatility of related dianion **5** alkylation reactions.[23]

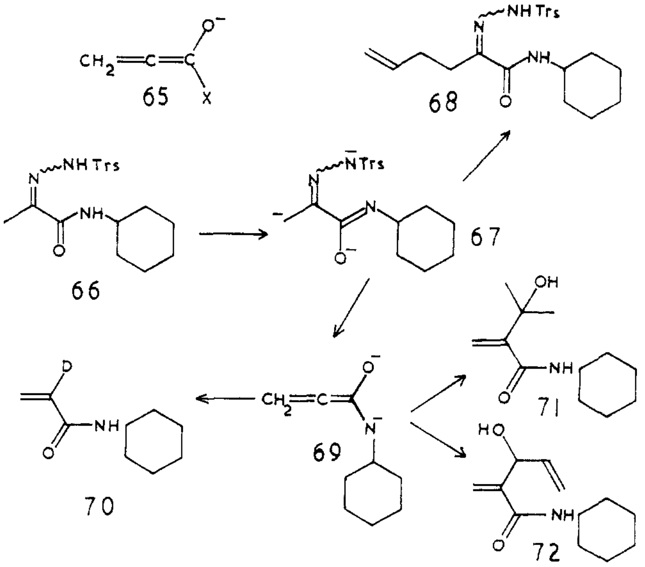




62 63 64

α-Keto Amides and the Shapiro Reaction

The propenoic acid anion derivatives (**65**) are most useful for the introduction of acrylate functionality.[24]



---

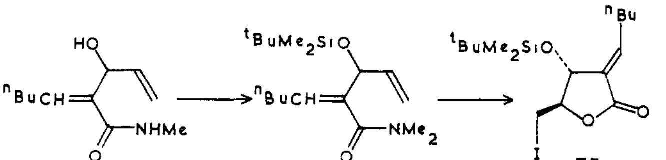
(21) R. M. Adlington and A. G. M. Barrett, *J. Chem. Soc., Chem. Commun.*, 1071 (1978).

(22) R. M. Adlington and A. G. M. Barrett, *J. Chem. Soc., Chem. Commun.*, 1122 (1979).

(23) F. T. Bond and R. A. DiPietro, *J. Org. Chem.*, 46, 1315 (1981); A. R. Chamberlin and F. T. Bond, *Synthesis*, 44 (1979).

We considered that these synthons should be available from α-keto carboxylic acids by the Shapiro reaction. Although pyruvic acid and its ethyl ester could be converted into the derived trisylhydrazones, neither could be converted into **65** (X = O^-, OEt).

However, secondary α-keto amides were excellent precusors for **65** (X = alkyl-N^-).[25] *N*-Cyclohexyl-2-oxopropanamide, which is readily available from cyclohexyl isocyanide and acetyl chloride[26] or from cyclohexylamine and 2-oxopropanoyl chloride, condensed cleanly with trisylhydrazine, giving the derivative **66** as a single geometric isomer. In DME solution at −78 °C, this was smoothly metalated with *n*-BuLi to give the trianion **67** as an intense orange solution. This was authenticated by allylation ($CH_2{=}CHCH_2Br$), giving **68** (70%). Alternatively, on warming up to 25 °C the orange color faded, nitrogen was evolved, and dianion **69** precipitated as a pale yellow solid. This dianion (**69**) could be intercepted with several electrophiles. Thus, for example, the addition of D_2O, acetone, and propenal gave **70** (54%), **71** (59%), and **72** (81%), respectively.[25] The reaction was readily extended to substituted acrylamides, for example, **73**.

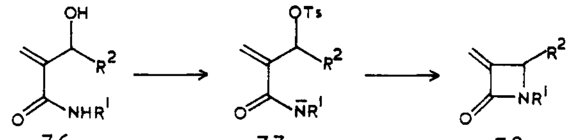


73 74 75

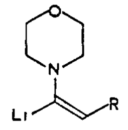
During synthetic studies on **51**, we examined the conversion of **73** into **75**. Reaction of **73** with *n*-BuLi, *t*-$BuMe_2SiCl$, and MeI in sequence gave **74** (77%). This amide (**74**), but not **73**, was readily transformed ($NaHCO_3$, KI_3) into the trans iodo lactone (**75**) (70%).

3-Methyleneazetidin-2-one Synthesis

3-Methyleneazetidin-2-one and derivatives (**78**) are potential precursors for analogues of the carbapenem antibiotics. We considered that the allenic dianions including **69** should be ideal precursors: thus the hydroxy enamides **76** were reacted with *n*-BuLi at −78 °C in THF and quenched with 4-toluenesulfonyl chloride at 25 °C. Rapid O-tosylation was followed by cyclization to give the α-methylene β-lactams (**78**, R^1 =cyclohexyl, $PhCH_2$; R^2 =alkyl, etc.) in yields of 19–68%.[27]



76 77 78



79

Conclusion

The Shapiro reaction provides a convenient method to convert ketones simply and in high yield into a plethora of olefinic substances. Many of these products, including vinylsilanes, nitro olefins, vinyl sulfides, and functionalized acrylic acid derivatives, are all most useful for further synthetic manipulations. The unique reactivity of ketone trisylhydrazones permits the facile synthesis of unsaturated lactone and lactam derivatives. The generation of unusual reactive intermediates including **69** and the Baldwin acyl anion equivalent **79**[28] should encourage further applications of trisylhydrazone chemistry. Without any doubt the Shapiro reaction is a colorful and versatile highway in organic synthesis.

We thank both the SERC and ICI Pharmaceuticals Division for financial support. In addition, we are most grateful for the experimental contributions from Peter Quayle and Andrew Walker as cited in the references.

---

(24) For example see J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 675 (1979); 3897 (1975); S. W. Rollinson, R. A. Amos, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **103**, 4114 (1981).

(25) R. M. Adlington and A. G. M. Barrett, *J. Chem. Soc., Chem. Commun.*, 65 (1981); *Tetrahedron*, **37**, 3935 (1981).

(26) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 1116 (1961).

(27) R. M. Adlington, A. G. M. Barrett, P. Quayle, A. Walker, and M. J. Betts *J. Chem. Soc., Chem. Commun.*, 404 (1981).

(28) J. E. Baldwin and J. C. Bottaro, *J. Chem. Soc., Chem. Commun.*, 1121 (1981).