First Example of a High-Yield Shapiro Reaction with a Substrate Containing Only Tertiary α-Carbon Atoms

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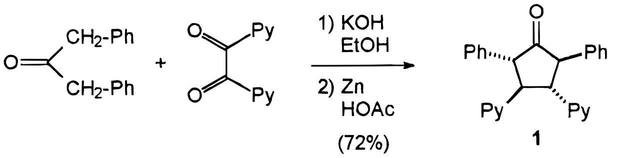
The Shapiro reaction provides a very useful method of transforming aldehydes and ketones to alkenes.[1] This is usually achieved by the reaction of the respective tosylhydrazone with at least 2 equiv of a strong base (typically an alkyllithium or lithium dialkylamide reagent) and subsequent aqueous workup. In contrast to the related Bamford−Stevens reaction, the Shapiro reaction is carried out under very mild conditions and normally gives high yields of alkenes without rearrangements or other side reactions.[1b] The mechanism involves deprotonation of the hydrazone NH and subsequently of an α-CH group; the resultant dianion eliminates first *p*-toluenesulfinate and then N_2.

The Shapiro reaction does not work well with substrates which contain only tertiary α-carbon atoms[2] because the formation of the dianionic intermediate is problematic in these cases and substitution at the imino carbon atom competes effectively with elimination.[3] Kolonko and Shapiro have described an optimized procedure for the conversion of tosylhydrazones into the corresponding trisubstituted alkenes by using ca. 2.5 equiv of LDA as base and TMEDA as the preferred solvent.[4] Although this gives moderate product yields in a few cases,[4] in other cases, the desired alkene is formed only in trace amounts.[5] We here report the first example of a high-yield Shapiro reaction with a substrate which contains only tertiary α-carbon atoms.

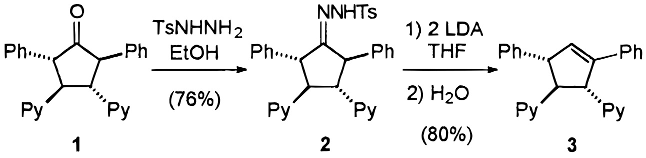
In the course of our program concerning the chemistry of pyridyl- and oligopyridyl-substituted cyclopentadienes,[6] the cyclopentanone **1** was prepared (Scheme 1). This compound had previously been believed to be 2,5-diphenyl-3,4-di(2-pyridyl)cyclopent-3-enone.[7]

Scheme 1. Synthesis of 1[a]



[a] Py = 2-pyridyl. Only one enantiomer of **1** is shown.

Scheme 2. Synthesis of 3[a]



[a] Only one enantiomer is shown.

1 was obtained in 72% yield as a single diastereomer according to NMR spectroscopic data. In the ^{1}H NMR spectrum, the four protons of the cyclopentanone moiety give rise to a highly symmetric 2 × 6 line multiplet indicative of an AA′XX′ spin system,[8] which is compatible with diastereomers which have molecular C_2 or C_s symmetry on the NMR time scale. From the crystal structure of the cyclopentene **3** (vide infra), the C_2 symmetric *all-trans* isomer (mixture of two enantiomers) shown in Scheme 1 can be inferred.

The Shapiro reaction proved to be the most convenient way of introducing the first double bond into the five-membered ring (Scheme 2). The tosylhydrazone **2** was obtained in 76% yield. For its conversion to the cyclopentene **3** it is essential to use LDA as deprotonating agent, since with *n*-BuLi mainly a Ziegler type reaction occurs.[9] Two equivalents of LDA is quite sufficient to obtain the trisubstituted alkene in an unprecedentedly high yield (80%). The double bond is introduced regiospecifically. A single diastereomer is isolated according to NMR spectroscopy. The structure of **3** was investigated by a single-crystal X-ray diffraction study,[10] which clearly shows the cyclopentene double bond to be in the position expected for a non-rearranged product (Figure 1); the aromatic substituents on the three tertiary carbon atoms of the cyclopentene ring are found to be mutually *trans*.

The C(3)−C(4) bond length is 133.6(2) pm corresponding to a double bond, whereas the four C−C single-bond lengths in the five-membered ring are in the range between 150.0(2) and 156.3(2) pm. The best plane of the phenyl ring attached to the sp^2 carbon atom C(3) forms an angle of only 20.2° with the plane defined by C(2), C(3), and C(4), indicative of a conjugative π-interaction between this phenyl group and the C(3)−C(4) double bond.

The reason for the smooth and swift Shapiro reaction observed in the case of **2** is most likely related to the high acidity of the benzylic α-hydrogen atoms leading to facile formation of the dianion. Notably, of the few cases described in the literature, the tosylhydrazone of 1,2-diphenyl-1-propanone, which also contains a tertiary

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[†] Crystal structure determination.

[1] For reviews, see: (a) Adlington, R. M.; Rarrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55. (b) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. For an overview concerning recent advances in the generation and chemistry of the vinyllithium intermediate, see: (c) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1. For a catalytic version of the reaction, see: (d) Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 2289.

[2] (a) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, 1811. (b) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 2801. (c) Bessière-Chrétien, Y.; Bras, J.-P. *C. R. Acad. Sci., Ser. C* **1969**, *268*, 2221.

[3] For a discussion of this point, see ref 2a.

[4] Kolonko, K. J.; Shapiro, R. H. *J. Org. Chem.* **1978**, *43*, 1404.

[5] See, for example: (a) Mohamadi, F.; Collum, D. B. *Tetrahedron Lett.* **1984**, *25*, 271. (b) Mueller, R. H.; Thompson, M. E.; DiPardo, R. M. *J. Org. Chem.* **1984**, *49*, 2217.

[6] (a) Siemeling, U.; Vorfeld, U.; Neumann, B.; Stammler, H.-G. *Chem. Ber.* **1995**, *128*, 481. (b) Siemeling, U.; Neumann, B.; Stammler, H.-G. *Z. Naturforsch. Teil B: Chem. Sci.* **1994**, *49*, 683. (c) Siemeling, U.; Vorfeld, U.; Neumann, B.; Stammler, H.-G. Manuscript in preparation.

[7] Bergmann, P.; Paul, H. *Chem. Ber.* **1967**, *100*, 828. Apart from microanalytical data, the authors only report mp 144 °C and ν(CO) 1740 cm^{-1}, which is virtually identical to the values found for compound **1**, whose structure was firmly established by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

[8] Friebolin, H. *Ein- und zweidimensionale NMR-Spektroskopie*, 2nd ed.; VCH: Weinheim, 1992; p 121.

[9] Ziegler, K.; Zeiser, H. *Chem. Ber.* **1930**, *63*, 1847.

[10] The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

S0022-3263(96)01737-9 CCC: $14.00

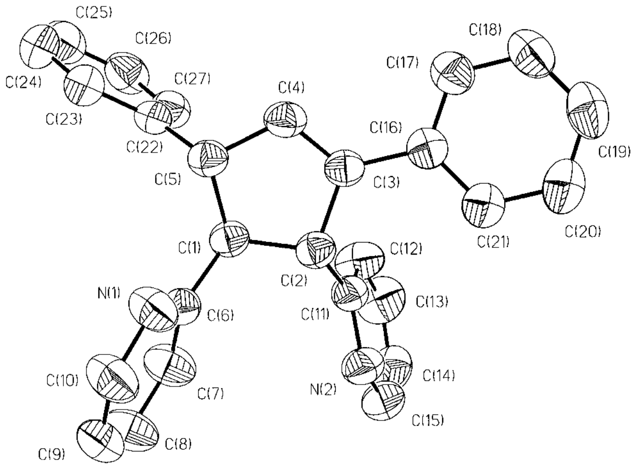

Figure 1. Molecular structure of **3** (ORTEP representation of one enantiomer with crystallographers' atom-numbering scheme). The substituents at C(1), C(2), and C(5) are oriented mutually *trans*. The alkene double bond is between atoms C(3) and C(4).

benzylic α-carbon atom, gave by far the best yield of the corresponding trisubstituted alkene.[4]

Experimental Section

All reactions were performed in an inert atmosphere (purified argon) by using standard Schlenk and cannula techniques; the workup was performed in the air. Solvents were appropriately dried and purified by using standard procedures. 2,2′-Pyridil, dibenzyl ketone, and tosylhydrazine were purchased from Aldrich and used as received. Elemental analyses were performed by the Microanalytical Laboratory of the Universität Bielefeld.

2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentanone (1). The procedure described by Bergmann and Paul[7] gave very unsatisfactory yields in our hands and was therefore modified considerably. Powdered KOH (ca. 2.0 g, ca. 36 mmol) was added to a vigorously stirred solution of 2,2′-pyridil (25.1 g, 118 mmol) and dibenzyl ketone (33.2 g, 158 mmol) in ethanol (400 mL). After 1 h the voluminous white precipitate was filtered off with suction, washed with ethanol (3 × 30 mL), and dried in vacuo. The resultant white powder (47.5 g) was suspended in acetic acid (286 mL, 300 g, 5.00 mol). The mixture was refluxed for 20 min giving a clear red solution. Zinc powder (31.0 g, 474 mmol) was added, whereupon the solution turned yellow. The mixture was refluxed for 30 min with stirring and filtered into water (150 mL) while still hot. The stirred mixture was cooled in an ice bath, and an ice-cold solution of NaOH (200 g, 5.00 mol) in water (ca. 500 mL) was added in small portions over a period of 1 h. The mixture was extracted with dichloromethane (4 × 300 mL). The combined extracts were dried with sodium sulfate and filtered through a 1 cm pad of silica gel to remove traces of a dark polar material. The solvent was removed in vacuo, and the remaining off-white solid was recrystallized from ethanol−water (3:1) yielding **1** (30.0 g) as colorless crystals. Slow evaporation of the mother liquor afforded a second crop (3.1 g), total yield 72%: mp 146 °C; IR 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02−4.11 (m, 2 H), 4.39−4.48 (m, 2 H), 6.57−6.60 (m, 2 H), 7.02−7.06 (m, 2 H), 7.13−7.32 (m, 12 H), 8.60−8.63 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 56.6, 62.1, 122.0, 124.7, 127.0, 128.4, 128.7, 136.0, 137.2, 149.7, 158.4, 213.7; MS *m/z* (%) 390 (47) [M^+]. Anal. Calcd for $C_{27}H_{22}N_2O$: C, 83.04; H, 5.67; N, 7.17. Found: C, 82.95; H, 5.54; N, 7.18.

2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentanone Tosylhydrazone (2). A solution of **1** (30.0 g, 76.8 mmol) and tosylhydrazine (17.0 g, 91.2 mmol) in ethanol (300 mL) was refluxed for 2 days with continuous removal of water by 3 Å molecular sieves. The solution was allowed to cool to room temperature. The precipitate was filtered off and washed with ethanol (2 × 20 mL). A second crop was obtained by reducing the volume of the combined mother liquor and washings to ca. 80 mL. The solid was dried in vacuo (10^{-3} mbar) at 80 °C for 1 day yielding **2** (32.5 g, 76%) as an ocher powder: ^1H NMR ($CDCl_3$) δ 1.23 (s, 1 H), 2.44 (s, 3 H), 3.67−3.81 (m, 2 H), 4.49−4.63 (m, 2 H), 6.37−6.44 (m, 2 H), 6.94−6.98 (m, 3 H), 7.03−7.07 (m, 4 H), 7.14−7.28 (m, 9 H), 7.42−7.44 (m, 2 H), 8.51−8.53 (m, 1 H), 8.60−8.62 (m, 1 H). Anal. Calcd for $C_{34}H_{30}N_4O_2S$: C, 73.09; H, 5.41; N, 10.02. Found: C, 72.88; H, 5.42; N, 9.95.

Table 1. Crystal Data and Structure Solution and Refinement for the Cyclopentene 3[a]

empirical formula	$C_{27}H_{22}N_2$
formula weight	347.47
crystal color	yellow
crystal size	1.50 × 0.90 × 0.50 mm
temperature	293(2) K
wavelength	0.71073 Å
space group	*C*2/*c*
unit cell dimensions	$a = 21.360(7)$ Å, $\alpha = 90°$ $b = 9.167(3)$ Å, $\beta = 98.59(3)°$ $c = 20.888(7)$ Å, $\gamma = 90°$
volume	4044(2) $Å^3$
Z	8
density (calcd)	1.230 g/cm^3
absorption coefficient	0.072 mm^{-1}
F(000)	1584
θ range for data collection	1.97−27.57°
index ranges	$0 \leq h \leq 27, 0 \leq k \leq 11, -27 \leq l \leq 26$
reflections collected	4680
independent reflections	4566 ($R_{int} = 0.0234$)
absorption correction	none
data/restraints/parameters	4560/0/350
final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0505$ for 3102 reflections $R_{w2} = 0.1198$
R indices (all data)	$R_1 = 0.0811$ $R_{w2} = 0.1395$
largest diff peak and hole	0.1 and −0.1 $eÅ^{-3}$
scan type	ω scan
scan range	1.2° in ω around $K\alpha_{1,2}$ maximum
programs used	Siemens SHELXTL plus, SHELXL-93
structure solution	direct
structure refinement	full-matrix least-squares on F^2
structure factor source	*International Tables*, Vol. C

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $R_{w2} = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$. Weighting scheme: calcd $w = 1/[s^2(F_o)^2 + (0.0593P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.

1,3-Diphenyl-4,5-di(2-pyridyl)cyclopentene (3). A solution of LDA, prepared at 0 °C from *i*-Pr_2NH (11.0 g, 109 mmol) and *n*-BuLi (69.0 mL of a 1.58 M solution in hexane, 109 mmol) in THF (200 mL), was added dropwise with stirring to a solution of **2** (30.2 g, 54.0 mmol) in THF (300 mL). During the second half of the addition, the violet mixture warmed slightly and gas evolution was observed. After stirring of the mixture for 14 h at room temperature, a saturated aqueous solution of sodium chloride (200 mL) was added dropwise with stirring at 0 °C. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried with Na_2SO_4. Volatile components were removed in vacuo leaving an ocher solid, which was recrystallized from ethanol−water (19:1) affording **3** (16.2 g, 80%) as yellow cubes in two crops: ^1H NMR ($CDCl_3$) δ 3.61 ("t", 1 H), 4.59 (m, 1 H), 5.06 (m, 1 H), 6.39 (t, J = 2.2 Hz, 1 H), 6.63−6.65 (m, 1 H), 6.96−7.00 (m, 1 H), 7.07−7.34 (m, 12 H), 7.40−7.48 (m, 2 H), 8.43−8.45 (m, 1 H), 8.68−8.70 (m, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 57.4, 61.3, 66.3, 121.2, 121.7, 122.8, 123.9, 126.5, 126.6, 126.9, 127.7, 128.1, 128.5, 131.2, 135.7, 136.2, 136.4, 143.9, 144.4, 149.3, 149.8, 161.5, 163.5. Anal. Calcd for $C_{27}H_{22}N_2$: C, 86.59; H, 5.92; N, 7.48. Found: C, 86.45; H, 5.81; N, 7.50.

Structure Determination. Crystals suitable for a single-crystal X-ray crystal structure determination were grown by slow cooling of a hot ethanol solution of the cyclopentene **3**. Details concerning crystal data and structure solution and refinement are collected in Table 1.

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