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Two Methods for the Preparation of 2-Cyclohexenones from Resin-Bound 1,3-Cyclohexanedione

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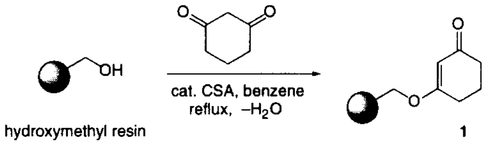
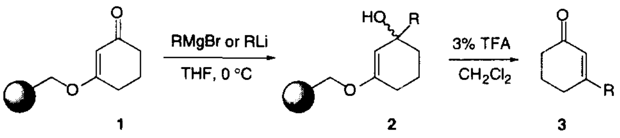
Abstract: The addition of organolithium or Grignard reagents to vinylogous ester resin **1** followed by mild hydrolysis of product resins **2** provides 3-alkyl-2-cyclohexenones in high purity (>95%). Alternatively, conversion of **1** to vinyl triflate resin **4** followed by palladium-mediated couplings with aryl boronic acids and hydrolysis furnishes 3-aryl-2-cyclohexenones in lower yield, but exceptional purity. © 1997 Elsevier Science Ltd.

Solid-phase synthesis has become a powerful tool in the preparation of combinatorial libraries of small molecules for drug lead discovery. A wide range of molecules can now be prepared by this technique due to the development of new solid-phase transformations.[1] We have focused part of our research effort on adapting various carbon-carbon bond forming reactions for use on solid support. We describe herein our investigation of organolithium and Grignard addition reactions of resin-bound vinylogous ester **1** and Suzuki cross-coupling reactions of vinyl triflate **4** as methods for the synthesis of 2-cyclohexenones.[2]

For practical purposes, we chose the inexpensive hydroxymethyl polystyrene resin as our solid support and attached 1,3-cyclohexanedione through a vinylogous ester linkage. Thus, heating a suspension of the resin with 1,3-cyclohexanedione (10 equiv) and a catalytic amount of camphorsulfonic acid in benzene with azeotropic removal of water furnished resin **1** (IR νC=O: 1652 cm^{-1}).





Treatment of a suspension of **1** with an organolithium or Grignard reagent (5 equiv, see Table 1) in anhydrous THF at 0 °C provided resin **2**. Brief exposure of **2** to a solution of 3% TFA in CH_2Cl_2 liberated enone **3** from the support in moderate to high yield and in excellent purity. Moderate yields of **3** were obtained with the more basic organolithium reagents (entries 1-3), presumably due to competing enolization of the vinylogous ester which precludes formation of **2**. Despite incomplete conversion of **1** to **2** in these cases, only enone **3** was released from the support following exposure to the mild cleavage conditions while 1,3-cyclohexanedione remained bound as determined by IR analysis. Typically, secondary organolithium and

Grignard reagents gave poor yields of impure **3**. To further examine the scope of this methodology, we loaded 5-methyl-1,3-cyclohexanedione and 1,3-cyclopentanedione onto hydroxymethyl polystyrene resin in similar fashion. Treatment of the resultant resins with *p*-tolylmagnesium bromide followed by cleavage from the support cleanly afforded 3-(*p*-tolyl)-5-methyl-2-cyclohexenone and 3-(*p*-tolyl)-2-cyclopentenone in 95% and 54% yield, respectively.

Table 1. Organolithium and Grignard reagents employed in the preparation of **3**.[3]

Entry	RMgBr or RLi	Yield of **3** (%)	Purity (%)
1.	MeLi	57	>95
2.	*n*-BuLi	59	>95
3.	PhLi	46	>95
4.	PhMgBr	80	>95
5.	*p*-tolylMgBr	86	>95
6.	PhC≡CLi	84	>95
7.	TMSC≡CLi	69	>95
8.	PhC≡CMgBr	55	>95
9.	vinylMgBr	55	80
10.	EtMgBr	80	>95
11.	*n*-pentylMgBr	65	>95
12.	isobutylMgBr	34	80
13.	benzylMgBr	40	>95

We next investigated Suzuki cross-coupling reactions of vinyl triflate resin **4**, prepared by treatment of a suspension of resin **1** with potassium hexamethyldisilazide (5.0 equiv) in THF at –78 °C and trapping of the resultant enolate with *N*-phenyltrifluoromethanesulfonimide (5.5 equiv).[4] The extent of conversion of **1** to **4** was difficult to monitor by IR analysis due to the overlap of respective C=O and C=C bands. Nevertheless, heating a deoxygenated suspension of resin **4** and excess boronic acid (7 equiv, see Table 2) under standard coupling conditions provided resin **5**.[5] Treatment of **5** with a solution of 5% TFA in acetone furnished enone **6** in moderate yield,[6] but exceptional purity. As described in our first method, only the desired enone product is liberated from the resin upon exposure to the cleavage conditions. To the best of our knowledge, this represents the first reported example of a palladium-mediated reaction of a resin-bound vinyl triflate.[7]

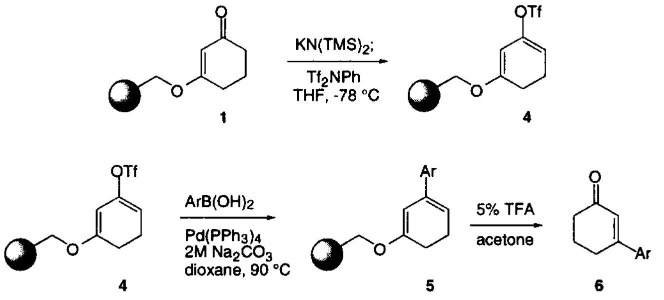


Table 2. Aryl boronic acids employed in the preparation of **6**.[3]

Entry	Ar	Yield of **6** (%)	Purity (%)
1.	Ph	35	>95
2.	3-CH_3OPh	30	>95
3.	3-CF_3Ph	38	>95
4.	4-CH_3OPh	23	>95
5.	3-ClPh	43	>95
6.	4-CHOPh	47	>95
7.	2-naphthyl	40	>95
8.	2-benzo[b]furanyl	28	>95
9.	3-thienyl	42	>95

In summary, we have developed two complementary solid-phase methods for the synthesis of 2-cyclohexenones. Noteworthy are the direct attachment of cyclic 1,3-diones to hydroxymethyl polystyrene resin, the development of two new solid-phase carbon-carbon bond forming reactions, and the mild and selective hydrolysis of the acid-labile intermediate resins to provide the product enones in high purity.

Representative Experimental Procedures

Preparation of resin 1 and the synthesis of 3-(*p*-tolyl)-2-cyclohexenone: A suspension of hydroxymethyl resin (0.99 mmol/g, 5.00 g, 4.95 mmol, 1 equiv), 1,3-cyclohexanedione (5.6 g, 50 mmol, 10 equiv), camphorsulfonic acid (25 mg, catalytic amt.), and 5-10 teflon boiling chips in benzene (150 ml) was heated at reflux with azeotropic removal of H_2O (Dean-Stark apparatus) for 16 h. The resin was filtered and washed successively with THF and CH_2Cl_2. The resin was dried in vacuo to provide 5.25 g (0.943 mmol/g) of light yellow resin **1**: FTIR (KBr, νC=O) 1652 cm^{-1} (strong, broad). A solution of *p*-tolylmagnesium bromide in ether (1.0 M, 0.850 mL, 0.850 mmol, 4.50 equiv) was added to a suspension of resin **1** (200 mg, 0.189 mmol, 1 equiv) in THF (2 mL) at 0 °C. The mixture was warmed to 23 °C and stirred gently for 2 h. Half-saturated aqueous ammonium chloride solution (5 mL) was added, and the resin was filtered and washed repeatedly with H_2O, THF, and CH_2Cl_2. The resin was partially dried under a stream of argon (5 psi), then treated with a solution of 3% TFA in CH_2Cl_2 (5 mL) and stirred for 20 min. The resin was filtered and washed with CH_2Cl_2 (2 x 5 mL). The combined filtrate was concentrated, and residual TFA was then removed by azeotropic distillation from toluene (2 x 5 mL) to afford 3-(*p*-tolyl)-2-cyclohexenone as a colorless oil (30 mg, 86% based on theoretical loading): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.1 Hz), 6.53 (s, 1H), 2.81 (t, 2H, J = 6.0 Hz), 2.55 (t, 2H, J = 6.7 Hz), 2.39 (s, 3H), 2.16 (qt, 2H, J = 6.3 Hz); FTIR (neat, νC=O) 1661 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_{14}O_1$ $(M)^+$ 186.1045, found: 186.1045.

Preparation of vinyl triflate resin 4 and synthesis of 3-(4-formylphenyl)-2-cyclohexenone: A solution of potassium hexamethyldisilazide in toluene (0.5 M, 7.33 mL, 3.67 mmol, 5.00 equiv) was added to a suspension of resin **1** (0.733 mmol/g, 1.00 g, 0.733 mmol, 1 equiv) in THF (20 mL) at –78 °C, and the resulting bright yellow suspension was stirred for 45 min. *N*-Phenyltrifluoromethanesulfonamide (1.43 g, 4.00 mmol, 5.46 equiv) was added, and the mixture was warmed to 23 °C and stirred for 2 h. The resultant brown resin was filtered and washed successively with THF, saturated aqueous $NaHCO_3$ solution, H_2O, THF, and CH_2Cl_2. The resin was dried in vacuo to provide 1.15 g (0.637 mmol/g) of light brown resin **4**: FTIR (KBr, νC=C) 1655 cm^{-1} (weak). A deoxygenated solution of $Pd(PPh_3)_4$ in dioxane (0.0090M, 10 mL, 0.090 mol, 0.67 equiv) was added to a deoxygenated suspension of resin **4** (208 mg, 0.132 mmol, 1 equiv) and 4-formylphenylboronic acid (135 mg, 0.900 mmol, 6.82 equiv) in aqueous 2M Na_2CO_3 solution (1 mL, 2.0 mmol, 15 equiv). The mixture was heated under argon (balloon) at 90 °C for 2.5 h. The resin was filtered and washed repeatedly with H_2O, THF, CH_3OH, and CH_2Cl_2, then treated with a solution of 5% TFA in acetone (2.5 mL) and stirred for 30 min. The resin was filtered and washed with CH_2Cl_2 (2 x 5 mL). The combined filtrate was concentrated, and residual TFA was then removed by azeotropic distillation from toluene (2 x 5 mL) to afford 3-(4-formylphenyl)-2-cyclohexenone as a colorless oil (12.4 mg, 47% based on theoretical loading): ^1H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.93 (d, 2H, *J* = 8.1 Hz), 7.68 (d, 2H, *J* = 8.2 Hz), 6.49 (s, 1H), 2.81 (t, 2H, *J* = 5.4 Hz), 2.54 (t, 2H, *J* = 6.7 Hz), 2.16 (qt, 2H, *J* = 6.3 Hz); FTIR (neat, νC=O) 1665 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_{12}O_2$ $(M)^+$ 200.0837, found: 200.0809.

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2. Very few 3-substituted-2-cyclohexenones are commercially available despite their importance as building blocks in organic synthesis.
3. Yields of unpurified **3** and **6** are based on theoretical resin loading. Purity was determined by HPLC (Waters μBondapak™ C-18, 125 Å, 10μ column, 3.9 x 300 mm, gradient 5-95% CH_3CN in H_2O w/ 0.1% TFA over 20 min, detector λ = 215 nM) and ^1H NMR analysis. All products gave satisfactory ^1H NMR, FTIR, and HRMS spectra. Reactions were performed on approximately 200 mg of resin to afford 10-30 mg of enone. The Grignard addition sequence is amenable to scale-up: the reaction of entry 5 (Table 1) was performed using 2.0 g of resin **1** and furnished 230 mg of 3-(*p*-tolyl)-2-cyclohexenone (84% yield).
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6. The lower yields in the Suzuki cross-coupling pathway may be attributed in part to incomplete conversion of **1** to **4**. Prolonged exposure of **5** to the cleavage conditions failed to afford additional enone product.
7. For solid-phase Suzuki cross-coupling reactions of aryl iodides and bromides, see (a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177-9180. (b) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172. (c) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169-5171. For solid-phase Heck reactions of aryl iodides and bromides, see (a) Yu, K-L.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919-8922. (b) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5748-5749.

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