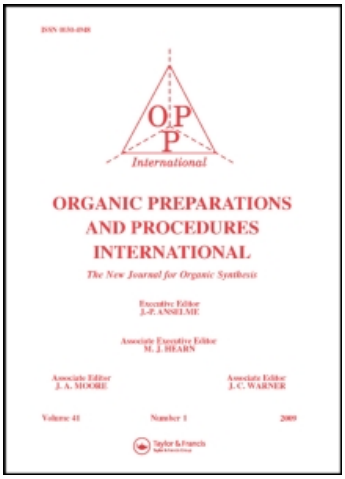

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THE SYNTHESIS OF *E*-2-(BROMOMETHYLENE)CYCLOHEXANONE AND *E*-2-(BROMOMETHYLENE)CYCLOHEPTANONE

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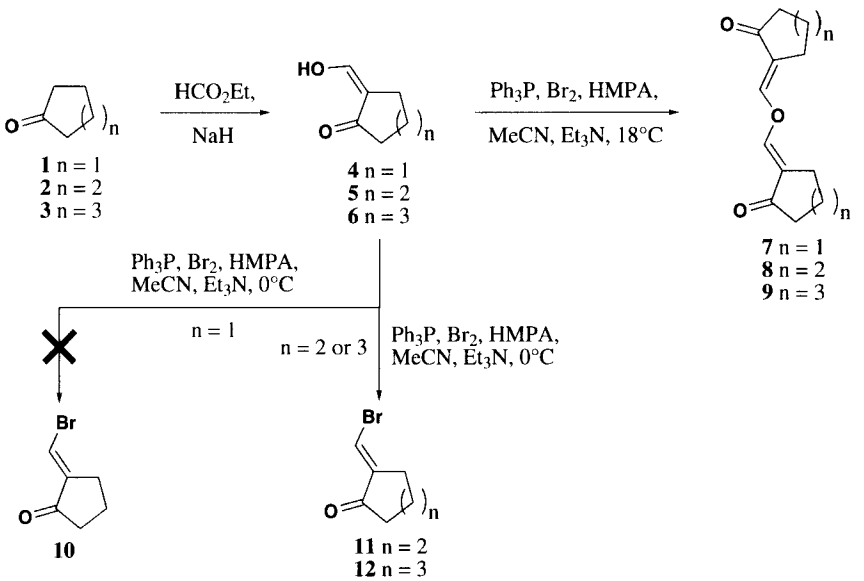
As part of an effort to exploit the Pd[0]-catalyzed Ullmann cross-coupling reaction[1,2] in the development of a new method for the synthesis of quinolines[3] we required access to the β–bromoenones **10–12**. Compound **11** has been reported previously[4] but a multi-step and atom-inefficient reaction sequence is involved and, consequently, this was not suitable for our purposes. On the other hand, the iodinated counterparts of targets **10** and **11** have been prepared in a straightforward manner by Piers and co-workers through reaction of the relevant 2-(hydroxymethylene)cycloalkanone, *viz.* compound **5** or **6**, with triphenylphosphine/molecular iodine in HMPA/acetonitrile/triethylamine mixtures at room temperature.[5] We sought, therefore, to apply such conditions in the preparation of compounds **10–12** and now report on the outcomes of our efforts in this regard.



Scheme 1

The requisite 2-(hydroxymethylene)cycloalkanones **4–6** were each synthesized, in 64%, 77% and 84% yields respectively, by reacting the corresponding cycloalkanone **1–3** with ethyl formate in the manner described by Eaton and Jobe[6] but using sodium hydride, rather than the more expensive potassium hydride, as base. In order to avoid formation of the aldol-type condensation product 2-cyclopentylidenecyclopentanone[7] from cyclopentanone the latter compound was added dropwise to a mixture of NaH and ethyl formate. The illustrated forms of compounds **4–6** are presented as such since they appear to represent the predominant tautomers but others as well as the corresponding *E*-isomers are probably present, at least to some extent. When each of compounds **4–6** was treated with triphenylphosphine/molecular bromine in HMPA/acetonitrile/Et_3N at *ca.* 18°C then the rather unstable ethers **7** (8%), **8** (15%) and **9** (27%), respectively, were obtained as the only characterizable products of reaction. The structure of each of these crystalline products follows from the usual range of spectroscopic studies. In addition, a single-crystal X-ray analysis was performed on the last of these compounds (**9**) which appears to be the only one of the three to have been reported previously.[8] Ethers **7–9** most likely arise through reaction of the initially formed target **10**, **11** or **12**, or some still oxygenated but now activated precursor thereof, with the corresponding 2-(hydroxymethylene)cycloalkanone in a nucleophilic addition/elimination sequence. Surprisingly, Piers *et al.*[5] do not comment on the formation of such compounds although our attempts to apply this group's protocols using compound **4** as a substrate for iodination, in fact gave ether **8** (*ca.* 14% at 88% conversion) and none of the reported β-iodoenone.

Despite the difficulties noted above, through the simple expedient of cooling the reaction mixture employed in the bromination of compounds **5** and **6** from *ca.* 18°C down to 0°C then ether formation could be completely suppressed and target compounds **11** and **12** were obtained, as single geometric isomers, in 51% and 95% yield, respectively. Unfortunately, this modification was not effective in providing access to target **10** as the previously observed ether **7** remained the only isolable product (17%) under such conditions. Further cooling of the reaction mixture simply resulted in the recovery of the starting material **4**. The somewhat unstable 2-(bromomethylene)cycloalkanones **11** and **12** were each purified by flash chromatography and obtained as clear, colorless and viscous oils. The derived NMR, IR and mass spectral (MS) data were in full accord with the assigned structures. In particular, the observed chemical shift (δ 7.20) of the resonance due to the olefinic proton in compound **12** is very close to that calculated (δ 7.19), using substituent additivity effects,[9] for that isomer incorporating an *E*-configured trisubstituted alkene moiety. The corresponding *Z*-isomer would be expected to exhibit an olefinic proton signal at *ca.* δ 6.95. By analogy, then, it is assumed the lower homologue, **11**, also incorporates the same *E*-double-bond geometry. The ^1H and ^{13}C NMR spectra of bromoalkenes **11** and **12** also revealed that each was contaminated by *ca.* 5–20% of the respective 2-(hydroxymethylene)cycloalkanone precursor. Despite this the title compounds participated effectively in Pd[0]-catalyzed Ullmann cross-coupling reactions with *o*-nitrobromobenzene.[3]

EXPERIMENTAL SECTION

General experimental procedures have been described elsewhere.[3]

2-(Hydroxymethylene)cycloalkanones 4–6. General Procedure.- A magnetically stirred mixture of sodium hydride (3.80 g of a 60% dispersion in mineral oil, 95 mmol) and ethyl formate (4.80 g, 58 mmol) in anhydrous ether maintained at 18°C was treated, dropwise, with the appropriate cycloalkanone (48 mmol). After 65 h the reaction mixture was poured, with stirring, into ice-water (100 g) and the pH of the ensuing mixture was adjusted to 1–2 using conc. HCl. The separated aqueous phase was extracted with ether (3 x 50 mL) and the combined organic phases were washed with NH_4Cl (1 x 200 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil.

(a) **2-(Hydroxymethylene)cyclopentanone (4)**.- The light-yellow oil obtained on reaction of cyclopentanone with ethyl formate was subjected to flash chromatography (silica, 5:95 v/v ethyl acetate/hexane) to afford, after concentration of the appropriate fractions (R_f 0.2 in 4:5:11 v/v/v ethyl acetate/dichloromethane/hexane), compound **4**[6] (64%) as light-grey crystalline solid, mp 71–73°C (*lit.*[6] mp 74.5–75°C). ^{1}H NMR ($CDCl_3$): δ 7.19 (s, 1H), 2.51 (t, J = 7.0 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H), 1.93 (m, 2H) (signal due to OH not observed); IR (NaCl): 3437, 2962, 2887, 1741, 1712, 1630, 1404, 1203, 1151, 1044 cm^{-1}; MS *m/z:* 112 ($M^{+\bullet}$, 53%), 84 (41), 83 (34), 55 (100), 39 (38); HRMS: $C_6H_8O_2$ requires $M^{+\bullet}$, 112.0524. Found $M^{+\bullet}$, 112.0520.

(b) **2-(Hydroxymethylene)cyclohexanone (5)**.- The light-yellow oil obtained on reaction of cyclohexanone with ethyl formate was subjected to flash chromatography (silica, 5:95 v/v ethyl acetate/hexane) to afford, after concentration of the appropriate fractions (R_f 0.4 in 1:5:11 v/v/v ethyl acetate/dichloromethane/hexane), compound **5**[10] (77%) as a clear, colorless and viscous oil. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, J = 2.5 Hz, 1H), 2.35 (m, 4H), 1.68 (m, 4H) (signal due to OH not observed); ^{13}C NMR ($CDCl_3$): δ 187.6 (CH), 184.9 (C), 108.9 (C), 31.2 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 21.2 (CH_2); IR (NaCl): 2940, 2862, 1713, 1635, 1600, 1448, 1408, 1371, 1314, 1194, 1160, 896 cm^{-1}; MS *m/z:* 126 ($M^{+\bullet}$, 19%), 98 (17), 88 (60), 73 (60), 70 (80), 61 (100), 55 (36); HRMS: $C_7H_{10}O_2$ requires $M^{+\bullet}$, 126.0681. Found $M^{+\bullet}$, 126.0681.

(c) **2-(Hydroxymethylene)cycloheptanone (6)**.- The light-yellow oil obtained on reaction of cycloheptanone with ethyl formate under the conditions specified above but only employing a 7 h reaction time was subjected to flash chromatography (silica, 8:92 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.4 in 1:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **6**[11] (84%) as a clear, colorless and viscous oil. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J = 8.8 Hz, 1H), 2.51 (m, 2H), 2.23 (m, 2H), 1.70 (m, 4H), 1.57 (m, 2H) (signal due to OH not observed); ^{13}C NMR ($CDCl_3$): δ 204.4 (C), 170.9 (CH), 114.7 (C), 42.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 24.7 (CH_2); IR (NaCl): 2927, 2854, 1640, 1584, 1451, 1434, 1406, 1264, 1220, 1089, 950 cm^{-1}; MS *m/z:* 140 ($M^{+\bullet}$, 100%), 125 (26), 111 (60), 83 (61), 81 (66), 70 (79), 55 (95); HRMS: $C_8H_{12}O_2$ requires $M^{+\bullet}$, 140.0837. Found $M^{+\bullet}$, 140.0835.

***E,E*-2,2'-(Oxydimethylidyne)dicycloalkanones 7–9. General Procedure**.- A magnetically stirred solution of triphenylphosphine (3.50 g, 13 mmol) and HPMA (4 mL) in acetonitrile (15 mL) maintained under a nitrogen atmosphere at 18°C was treated with molecular bromine (620 µL, 12 mmol) then triethylamine (Et_3N) (1.7 mL, 12 mmol). The resulting mixture was stirred at 18°C for 0.5 h then a solution of the relevant 2-(hydroxymethylene)cycloalkanone (10 mmol) in acetonitrile (2 mL) was added. The ensuing mixture was stirred at 18°C for the period specified below then diluted with dichloromethane (100 mL) and $NaHCO_3$ (150 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 x 30 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil.

(a) ***E,E*-2,2'-(Oxydimethylidyne)dicyclopentanone (7)**.- The light-yellow oil resulting from reaction of compound **4** under the conditions specified above and using a reaction time of 2 h was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.4 in 8:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **7** (8%) as a light-yellow and crystalline solid, mp 106–108°C. ^1H NMR ($CDCl_3$): δ 7.36 (s, 2H), 2.65 (m, 4H), 2.30 (m, 4H), 1.92 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 207.4 (C), 148.6 (CH), 120.4 (C), 39.1 (CH_2), 25.3 (CH_2), 20.0 (CH_2); IR (NaCl): 2963, 2898, 1718, 1664, 1626, 1412, 1175, 1006, 820 cm^{-1}; MS *m/z:* 206 ($M^{+\bullet}$, 37%), 177 (6), 150 (42), 111 (37), 96 (43), 95 (35), 67 (68), 55 (92), 41 (100); HRMS: $C_{12}H_{14}O_3$ requires $M^{+\bullet}$, 206.0943. Found $M^{+\bullet}$, 206.0940.

(b) ***E,E*-2,2'-(Oxydimethylidyne)dicyclohexanone (8)**.- The light-yellow oil resulting from reaction of compound **5** under the conditions specified above and using a reaction time of 48 h was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.3 in 4:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **8** (15%) as a light-yellow and crystalline solid, mp 136–138°C. ^1H NMR ($CDCl_3$): δ 7.44 (s, 2H), 2.53 (m, 4H), 2.38 (m, 4H), 1.81 (m, 4H), 1.71 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 200.0 (C), 151.1 (CH), 119.8 (C), 40.0 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 22.6 (CH_2); IR (NaCl): 2938, 2859, 1690, 1628, 1586, 1456, 1202, 1141, 1089, 908 cm^{-1}; MS *m/z:* 234 ($M^{+\bullet}$, 27%), 205 (52), 177 (33), 125 (100), 124 (70), 81 (58), 41 (78); HRMS: $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256. Found $M^{+\bullet}$, 234.1255.

(c) ***E,E*-2,2'-(Oxydimethylidyne)dicycloheptanone (9)**.- The light-yellow oil resulting from reaction of compound **6** under the conditions specified above and using a reaction time of 48 h was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.4 in 8:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **9**[8] (27%) as a light-yellow and crystalline solid, mp 85–86°C (*lit.*[8] mp 83–84°C). ^1H NMR ($CDCl_3$): δ 7.46 (s, 2H), 2.60 (m, 4H), 2.51 (m, 4H), 1.80–1.60 (complex m, 12H); ^{13}C NMR ($CDCl_3$): δ 203.8 (C), 151.4 (CH), 123.7 (C), 44.3 (CH_2), 31.6 (CH_2), 29.6 (CH_2), 25.3 (CH_2), 24.6 (CH_2); IR (NaCl): 2925, 2854, 1695, 1630, 1583, 1453, 1206, 1165,

1043, 942 cm^{-1}; MS *m/z:* 262 ($M^{+\bullet}$, 20%), 233 (73), 191 (45), 139 (48), 110 (70), 67 (75), 55 (100), 41 (85); HRMS: $C_{16}H_{22}O_3$ requires $M^{+\bullet}$, 262.1569. Found $M^{+\bullet}$, 262.1568.

***X-ray Crystal Data** for **9**:* M_r = 262.35, T = 200 K, triclinic space group $P\bar{1}$, a = 5.7933 (3) Å, b = 9.3824 (5) Å, c = 14.301 (1) Å, α = 96.195 (2)°, β = 99.548 (2)°, γ = 105.769 (5)°, V = 728.04 (8) $Å^3$, D_c (Z = 2) = 1.197 g cm^{-3}, λ(MoKα) = 0.71073 Å, analytical absorption correction, 3311 unique data ($2\theta \leq 55°$), 1811 with $I > 3\sigma(I)$; R = 0.0389, wR = 0.0424. Refinement was achieved using the CRYSTALS program package.[12] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 257496). These data can be obtained free-of-charge *via* www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

***E*-2-(Bromomethylene)cycloalkanones 11 and 12. General Procedure**.- A magnetically stirred solution of triphenylphosphine (2.20 g, 8.5 mmol) and HPMA (4 mL) in acetonitrile (14 mL) maintained under a nitrogen atmosphere at 0°C was treated with molecular bromine (400 µL, 8 mmol) then triethylamine (Et_3N) (1.1 mL, 8 mmol). The resulting mixture was stirred at 0°C for 0.5 h then a solution of the relevant 2-(hydroxymethylene)cycloalkanone (6.5 mmol) in acetonitrile (2 mL) was added and the resulting mixture allowed to warm to 18°C over a period of 0.5 h. The ensuing mixture was stirred at 18°C for 3 h then diluted with dichloromethane (80 mL) and $NaHCO_3$ (120 mL of a saturated aqueous solution). The organic phase was washed with $NaHCO_3$ (2 x 80 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil.

(a) ***E*-2-(Bromomethylene)cyclohexanone (11)**.- The light-yellow oil resulting from reaction of compound **5** under the conditions specified above was subjected to flash chromatography (silica, 4:96 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.5 in 1:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **11**[4] (51%) as a clear, light-yellow oil and contaminated with *ca.* 5–20% of precursor **5**. ^1H NMR ($CDCl_3$): δ 7.39 (t, J = 2.3 Hz, 1H), 2.56 (m, 2H), 2.42 (m, 2H), 1.90–1.50 (complex m, 4H); ^{13}C NMR ($CDCl_3$): δ 198.2 (C), 141.5 (C), 121.7 (CH), 40.1 (CH_2), 29.8 (CH_2), 23.4 (CH_2), 23.1 (CH_2); IR (NaCl): 2940, 2866, 1689, 1576, 1280, 1139, 802 cm^{-1}; MS *m/z:* 190 and 188 ($M^{+\bullet}$, 25 and 25%), 81 (100), 79 (86), 41 (75); HRMS: $C_7H_9{}^{79}BrO$ requires $M^{+\bullet}$, 187.9837. Found $M^{+\bullet}$, 187.9843.

(b) ***E*-2-(Bromomethylene)cycloheptanone (12)**.- The light-yellow oil resulting from reaction of compound **6** under the conditions specified above was subjected to flash chromatography (silica, 4:96 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f 0.5 in 1:5:11 v/v/v ethyl acetate/dichloromethane/hexane) then afforded compound **12** (95%) as a clear, light-yellow oil and contaminated with *ca.* 5–20% of precursor **6**. ^1H NMR ($CDCl_3$): δ 7.20 (d, J = 0.6 Hz, 1H), 2.53 (m, 4H), 1.75–1.50 (complex m, 6H); ^{13}C NMR ($CDCl_3$): δ 200.9 (C), 145.7 (C), 120.2 (CH), 43.2 (CH_2), 31.0 (CH_2), 30.0 (CH_2), 28.5 (CH_2), 25.0 (CH_2); IR (NaCl): 2928, 2856,

1689, 1640, 1583, 1452, 1300, 1164, 943 cm^{-1}; MS *m/z:* 205 and 203 [$(M+H)^+$, both 59%], 204 and 202 ($M^{+\bullet}$, 31 and 37), 123 (40), 95 (100), 81 (42); HRMS: $C_8H_{11}{}^{79}BrO$ requires $M^{+\bullet}$, 201.9993. Found $M^{+\bullet}$, 201.9989.

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