An Effective System to Synthesize Arylacetones. Substrate-ionic Liquid-ultrasonic Irradiation

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Manganese(III) acetate-promoted aromatic acetonylation has been accomplished with ultrasonic irradiation in ionic liquids, [*N*-*n*-pentyl-4-picolinium] [*closo*-$CB_{11}H_{12}$] (**1**), [OMIM] [BF_4] and [BMIM] [PF_6] in 62-93% yields, with excellent chemical selectivity.

Arylacetones are one of the most popular precursors to amphetamine and methamphetamine.[1] Among the various synthetic routes to these compounds, direct acetonylation of aromatic ring is potentially one of the most attractive methods. While the starting materials are readily obtainable and inexpensive, the low yields of such methods present drawbacks.[2] We have been interested in the use of ionic liquids as solvents for organic reactions. Their use in both dehalogenation and carbene-mediated reactions have resulted in increased yields and enhanced selectivity.[3] The ionic liquids, salts that are liquids at ambient temperatures, have received much attention as possible replacements for conventional solvents and as media for immobilizing transition metal catalysts in biphasic processes.[4,5] However, relatively little work has been done on the use of ionic liquids as reaction media for the single electron radical mediated reactions.[6] In order to explore the use of ionic liquids in providing high yield and regioselective synthesis routes to arylacetones, we have initiated an investigation of the manganese(III) acetate ($Mn(OAc)_3$)-promoted radical reactions of acetone and a number of arenes in the ionic liquids, 1-octyl-3-methylimidazolium tetrafluoroborate [OMIM][BF_4], 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6]. In addition, we report the synthesis and use of a new ionic liquid composed of *N*-*n*-pentylpicolinium cation ($[PPI]^+$) and icosahedral anion, 1-carba-*closo*-dodecaborate (1-) $[CB_{11}H_{12}]^-$. This anion is a weakly coordinating anion possessing no lone pairs of electrons and is oxidatively stable.[7] Herein we describe our initial results concerning this study.

The metathesis reaction of [PPI]Br (**2**)[8] with $Cs[CB_{11}H_{12}]$[9] in CH_2Cl_2 followed by purification with SiO_2 column chromatography, led to *N*-*n*-pentyl-4-picolinium carborane, [PPI][$CB_{11}H_{12}$] (**1**) in 94% yield.[10] The ^1H and ^{13}C NMR spectra of **1**, as well as the elemental analyses, are consistent with the formulation as given in the experimental. The ^{11}B NMR spectrum of **1** shows the expected 3 resonances in a 1:5:5 peak area ratios for the CB_{11} cage. Other than the strong $\nu_{B\text{-}H}$ absorption at 2538 cm^{-1}, the IR spectrum of **1** shows no noteworthy features and is presented for purposes of qualitative analysis. Compound **1** is an air-stable liquid that solidifies at 16 °C to give a colorless wax. The lower melting point of **1** is somewhat surprising in view of the 70 °C value reported for the 1-octyl-2-methylimidazolium salt of the [*closo*-$CB_{11}H_{12}]^-$.[11]

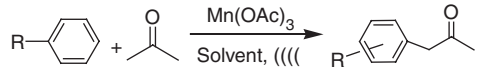
Arylacetones are prepared in a single step free-radical reaction between the particular arene, acetone and manganese(III) acetate ($Mn(OAc)_3$) in the solvents, **1**, [OMIM][BF_4], [BMIM][PF_6], and acetic acid.[12] In all cases, ultrasonic radiation and continuous stirring is used to facilitate distribution of substrates in the multiphase reaction media. The known products are confirmed by HPLC-MS analysis with a ZORBAX SB-C18 column and, for phenylacetone, by ^1H NMR spectroscopy. Irrespective of the arene, the chromatographic elution sequence for the substituted phenylacetone isomers was found to be: *ortho*-, *meta*-, *para*-. These results are consistent with the elution times found for structurally related analogues, such as substituted phenylacetic acids and substituted benzoic acids.[13] Table 1 lists the yields and product distributions found for the different solvents. In all cases, the yields were calculated based on the consumed $Mn(OAc)_3$, which was the limiting reagent. For comparison, several results of Kurz, and co-workers, who studied the acetonylation in acetic acid are also listed.[2] As can be seen from Table 1, the yields of the aryl acetones were solvent dependent, ranging from low of 62% for nitrophenylacetone in [BMIM][PF_6] to high of 93% for tolunylacetone in [PPI][$CB_{11}H_{12}$]. However, even the lowest yield in the ionic liquid system showed a significant improvement over those obtained in acetic acid media, which ranged from 23% to 53%. The effect of ultrasonic irradiation can be seen from the fact that for toluene in [BMIM][PF_6], the use of ultrasound increased the yield from 75% to 86%. In all cases, the isomer distribution of the products was *ortho*- $\gg$ *para*- $\geq$ *meta*- for any substituted arylacetone. The highest *o*-/*m*-/*p*-isomer ratio, 96.3:1.2:2.5, was found for nitrobenzene in the [PPI][$CB_{11}H_{12}$] solvent. This selectivity is comparable to 85/5/10 isomer ratio found by Strazzolini and coworkers from the nitration of phenylacetone.[14]

All of the ionic liquids can be recovered by extraction of the reaction residue with dichloromethane, followed by filtration and the removal of the solvent under reduced pressure.[12] The ionic liquids can be reused four times without any noticeable change in either yields or isomer ratios. The reduction product, manganese(II) acetate, can also be recovered during the extraction process of ionic liquid. The manganese(II) acetate can then be oxidized by potassium permanganate to regenerate manganese(III) acetate.[15]

In summary, we have synthesized a new ionic liquid, derived from the *N*-*n*-pentyl-4-picolinium cation and the 1-carba-*closo*-dodecaborate (1-) anion, having a melting point of 16 °C. The use of this, and several other ionic liquid solvents, in conjunction with ultrasonic irradiation, was found to enhance both yields and regioselectivity in the acetonylation reactions of

arenes mediated with manganese(III) acetate. The superior performance of this system warrants further mechanistic studies, which are currently underway in our laboratories.

Table 1. Synthesis of arylacetones



R	Yield[a] /%, total	Time /h	Product distribution *ortho-/meta-/para-%*
Me	A86, B84, C93, D[b]51, A[c]75	1.5	A80.4/8.7/10.9 B76.3/6.2/17.5 C84.7/2.8/12.5 D[b]66.0/19.0/15.0 A[c]77.2/11.3/11.5
NO_2	A62, B68, C77, D23	2.0	A83.3/4.8/11.9 B86.0/2.7/11.3 C96.3/1.2/2.5 D73.4/13.6/13.0
Cl	A64, B67, C79, D[b]25	1.5	A85.7/5.1/9.2 B82.9/6.8/10.3 C94.1/1.8/4.1 D[b]72.1/6.0/21.9
*t*Bu	A82, B87, C91, D53	2.0	A71.8/13.7/14.5 B65.7/16.1/18.2 C77.9/8.7/13.4 D68.9/17.4/13.7

[a]A = in [BMIM][PF_6], B = in [OMIM][BF_4], C = in [PPI][$CB_{11}H_{12}$], D = in acetic acid. The product distribution was measured with HPLC-MS (in a ZORBAX SB-C18 column) as well as ^{1}H NMR. [b]Ref. 2 results. [c]In A without ultrasonic irradiation.

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10 All synthetic procedures were carried out in argon atmosphere with standard Schlenk techniques. A 1.30 g (5.32 mmol) **2** dissolved in dry CH_2Cl_2 (24.0 mL) was added to a stirred solution of Cs[$CB_{11}H_{12}$] (1.50 g, 5.44 mmol) in 110.0 mL dry methanol. The mixture was stirred at room temperature for 24 h and then all solvents were evaporated under reduced pressure. The resulting viscous residue was dissolved in CH_2Cl_2 and purified by column chromatograph (SiO_2), CH_2Cl_2/Diethyl ether (v/v = 4/1) as the movable phase. Removal of the solvent under reduced pressure and drying under high vacuum for 2.5 days resulted in 1.54 g (94% yield) of [*N*-*n*-Pentyl-4-picolinium]$^+$[*closo*-$CB_{11}H_{12}$]$^-$ (**1**) isolated as a colorless colorless sticky liquid with the dynamic viscosity $\mu = 160$ cP (0.01 g·cm^{-1}·s^{-1}, on a CV-100 Caulking Viscometer at 20 °C, estimated error: ±2%), The liquid solidified at 16 °C to give **1** as a colorless waxy solid. Anal. Calcd for $C_{12}H_{30}B_{11}N$ (307.300): C, 46.90; H, 9.84; N, 4.56. Found: C, 46.83; H, 9.80; N, 4.52%. ^{1}H NMR ($CDCl_3$, ppm): δ 8.74 (d, 2H, 2 N-C_{Py}-H), 7.62 (d, 2H, C_{Py}-H), 4.46 (t, 2H, N-CH_2-), 2.41 (s, 3H, C_{Py}-CH_3), 1.75 (m, 2H, N-C-CH_2-), 0.95 (m, 4H, N-C-C-CH_2-CH_2-), 0.61 (t, 3H, -CH_3), 0.20-2.20 (m, 12H, 11 BH and C_{cage}H). ^{13}C NMR ($CDCl_3$, ppm): δ 13.78 (C-C-C-C-C-N), 22.05 (C-C-C-C-C-N or CH_3-C_{Py}), 22.31 (C-C-C-C-C-N, or CH_3-C_{Py}), 28.01 (C-C-C-C-C-N), 29.64 (C_{cage}), 31.36 (C-C-C-C-C-N), 61.44 (C-C-C-C-C-N), 129.13 (C_{Py}), 143.73 (C_{Py}), 159.33 (C_{Py}). IR (KBr pellet, cm^{-1}): 3416 (br, s), 2955 (s, s), 2927 (s, vs), 2858 (s, s), 2538 (vs, s, $\nu_{B\text{-}H}$), 1641 (s, s), 1572 (s, w), 1517 (s, m), 1468 (s, s), 1379 (s, w), 1173 (s, m), 1016 (br, m), 946 (s, w), 826 (s, s), 723 (s, m), 554 (s, w).
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12 Synthesis of arylacetone. In a typical reaction to prepare phenylacetone, a mixture of manganese(III) acetate dihydrate (0.80 g, 2.87 mmol), benzene (3.5 mL), acetone (3.5 mL) and ionic liquid 10.0 mL was irradiated with by ultrasound (ultrasonic frequency 50 kHz) for 1.5 h with continuous stirring under argon atmosphere. The dark brown color of manganese (III) acetate changed to the pale pink of manganese(II) acetate smoothly. At the end of this time, 2.0 mL methanol was added to the vessel to trap the reaction. The reaction mixture was fractionatedly distilled at **1** atmospheric pressure to recover unreacted benzene and the residue was extracted with dry diethyl ether (2 × 20 mL). The ether layer was separated and washed with 20.0 mL Na_2CO_3 to remove any trace of acetic acid (this process only for the case of acetic acid solvent was used). The ether was then dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuum. The residue was subjected to high vacuum distillation to remove any trace of ionic liquid solvent, the 86-87 °C/6.0 mmHg fraction was collected for phenylacetone to give the ^{1}H NMR pure phenylacetone 0.16 g (83% yield) when [PPI][$CB_{11}H_{12}$] was used as solvent. In [BMIM][PF_6] and [OMIM][BF_4], the yield was 73% and 79%, respectively. For substituted arylacetones, the resulting clear product mixture after high vacuum distillation process was subjected to HPLC-MS to determine the product yield and distribution. The detail HPLC conditions are: column ZORBAX SB-C18, 25 cm × 0.46 cm × 3.5 μm, flow rate 1.0 mL/min, temperature 25 °C, pressure 1680 psi, mobile phase acetonitrile/methanol (v/v = 9/1). The peak identity was confirmed by HPLC-MS and internal standard. Retention time (mins) and main MS peaks (*m/z*, abundance) of substituted phenylacetone as follow: (1) Methylphenylacetone, t_{ortho} = 13.8, t_{meta} = 16.1, t_{para} = 18.8, *m/z* = 148.0 (9), 105.0 (31), 43.0 (100), 15.0 (17), (2) Nitrophenylacetone, t_{ortho} = 7.3, t_{meta} = 11.2, t_{para} = 14.6, *m/z* = 179.0 (100), 136.0 (42), 91.0 (41), 77.0 (8), 43.0 (87), 30.0 (17), (3) Chlorophenylacetone, t_{ortho} = 9.2, t_{meta} = 13.4, t_{para} = 16.4, *m/z* = 170.0 (11), 168.0 (35), 127.0 (15), 125.0 (46), 91.0 (18), 43.0 (100), (4) *tert*-Butylphenylacetone, t_{ortho} = 12.4, t_{meta} = 14.7, t_{para} = 17.3, *m/z* = 190.0 (7), 147.0 (11), 43.0 (100), 15.0 (18).
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