Supplementary Material (ESI) for Chemical Communications

Supporting Information (3 pages)

The direct α-zincation of amides, phosphonates and phosphine oxides by H-Zn exchange

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General considerations. Standard Schlenk-line and glovebox techniques were used unless stated otherwise. N,N-Diisopropylacetamide (DIPA)[1], $ZnPh_2$[2] and $Zn[N(SiMe_3)]_2$[3] were prepared following literature procedures. N,N-Dimethylacetamide (DEA), dimethyl methylphosphonate, *tert*-butylamine, diethylamine, triethylamine, pyridine, diisopropylamine, piperidine, pyrrolidine, morpholine, and benzaldehyde were distilled from CaH_2 under N_2. 4-(Dimethylamino)pyridine, trimethylphospine oxide, $ZnEt_2$, and $ZnPh_2$ were purchased from commercial sources (Sigma-Aldrich, Alfa, Strem) and were used as received. Toluene, tetrahydrofuran (THF), and CH_2Cl_2 were passed through columns of activated alumina and sparged with N_2 prior to use. C_6D_6 was vacuum transferred from Na-benzophenone ketyl. CD_2Cl_2 was vacuum transferred from CaH_2. Chemical shifts (δ) for ^1H NMR spectra (400 and 500 MHz) are given relative to residual protium in the deuterated solvent at 7.16, 5.32, and 7.27 ppm for C_6D_6, CD_2Cl_2, and $CDCl_3$ respectively.

Sample Procedure for zincation of carbon acids (entry 10, Table 1). Toluene (2 mL), $ZnPh_2$ (40.0 mg, 0.182 mmol), DEA (11.3 μL, 0.091 mmol) and morpholine (8.0 μL, 0.091 mmol) were combined to form a homogeneous colorless solution. The solution was heated to 50 ºC for 24 h. The reaction mixture was cooled to ambient temperature and quenched with 99.9% D_2O (50 μL). The volatiles were evaporated under reduced pressure (0.5 mmHg) to afford a white residue which was extracted with $CDCl_3$ and filtered. ^1H NMR spectroscopic data indicated the presence of $CH_2DC(O)NEt_2$ and $CH_3C(O)NEt_2$ in a ratio of 10.2:1 (91% deuteration). All the reactions described in Tables 1 and 2 were performed analogously, but with variation of stoichiometry, substrate, zinc reagent, and amine. ^1H NMR spectroscopic data for the substrates and their deuterated derivatives follow. For the deuterated substrates, only the resonances that differ from those of the parent compound are listed.

$CH_3C(O)NEt_2$. ^{1}H NMR ($CDCl_3$): δ 3.39 (q, J = 7.0 Hz, 2H), 3.32 (q, J = 7.0 Hz, 2H), 2.10 (s, 3H, CH_3), 1.19 (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H). **$CH_2DC(O)NEt_2$.** ^{1}H NMR ($CDCl_3$): δ 2.08 (t, ^{2}J = 2.2 Hz, 2H, CH_2D).

$CH_3C(O)N^iPr_2$. ^{1}H NMR ($CDCl_3$): δ 3.90 (sept, J = 6.8 Hz, 1H), 3.5 (broad, 1H), 2.09 (s, 3H, CH_3), 1.37 (d, J = 6.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H). **$CH_2DC(O)N^iPr_2$.** ^{1}H NMR ($CDCl_3$): δ 2.08 (t, ^{2}J = 2.2 Hz, 2H, CH_2D).

$OPMe_3$. ^{1}H NMR ($CDCl_3$): δ 1.54 (d, J = 12.8 Hz, 9H). **$OPMe_2CH_2D$.** ^{1}H NMR ($CDCl_3$): δ 1.54 (d, J = 12.8 Hz, 6H), 1.52 (dt, J = 12.8 Hz, 2.0 Hz, 2H).

$CH_3(MeO)_2PO$. ^{1}H NMR ($CDCl_3$): δ 3.75 (d, J = 11.0 Hz, 6H, OMe), 1.49 (d, J = 17.5 Hz, 3H, CH_3). **$CH_2D(MeO)_2PO$.** ^{1}H NMR ($CDCl_3$): δ 1.47 (dt, J = 17.5 Hz, J = 2.0 Hz, 2H, CH_2D).

Reaction of zincated DEA with I_2. Toluene (10 mL) was added to $ZnPh_2$ (100 mg, 0.455 mmol), DEA (28.4 μL, 0.228 mmol) and morpholine (19.8 μL, 0.228 mmol) to form a colorless homogeneous solution. The solution was heated to 50 ºC for 24 h. At ambient temperature I_2 (0.577 g, 2.28 mmol) was added. The mixture was stirred for 1 h at room temperature. The solution was partitioned between 1 M $NaHSO_3$ (10 mL) and CH_2Cl_2 (15 mL). The organics were separated, washed with brine (10 mL) and dried over $MgSO_4$. The volatiles were evaporated and the residue was taken up in $CDCl_3$. ^{1}H NMR spectroscopic data revealed the product N,N-diethyl-2-iodoacetamide[4] and DEA in a ratio of 7.3:1 (88% conversion). This crude product contained essentially no (< 5% by NMR) other impurities. ^{1}H NMR (diethyl-2-iodoacetamide, $CDCl_3$): δ 3.72 (s, 2H), 3.38 (q, J = 7.2 Hz, 2H), 3.33 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).

Reaction of zincated DEA with benzaldehyde. Toluene (2 mL) was added to $ZnPh_2$ (40 mg, 0.182 mmol), DEA (11.3 μL, 0.091 mmol) and morpholine (8.0 μL, 0.091 mmol) to form a colorless homogeneous solution. The solution was heated to 50 ºC for 24 h. The reaction mixture was cooled to ambient temperature and benzaldehyde (9.3 μL, 0.091 mmol) was added. The resulting mixture was stirred for 12 h at room temperature. To the mixture was added 1,3,5-trimethoxybenzene (internal standard) (15 mg, 0.091 mmol). The solution was partitioned between saturated NH_4Cl (10 mL) and CH_2Cl_2 (10 mL). The organics were separated and dried

over $MgSO_4$. The volatiles were evaporated and the residue was taken up in $CDCl_3$. ^1H NMR spectroscopic data showed the addition product N,N-diethyl-3-hydroxy-3-phenylpropionamide[5] and 1,3,5-trimethoxybenzene in a ratio of 0.57:1.0 (57% yield). The reaction was repeated using 10 equivalents of benzaldehyde to give an improved yield of 78%. ^1H NMR (N,N-diethyl-3-hydroxy-3-phenylpropionamide, $CDCl_3$): δ 7.4-7.2 (mult, 2H, ArH), 5.14 (dd, J = 10 Hz, J = 2.5 Hz, 1H), 5.02 (d, J = 2.5 Hz, 1H, OH), 3.39 (mult, 2H), 3.23 (mult, 2H), 2.6 (ddd, J = 16 Hz, 9.5 Hz, 2.5 Hz), 1.15 (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 171.7, 143. 3, 128.7, 127.7, 126.0, 70.8, 42.1, 41.8, 40.5, 14.2, 13.2.

Reaction of $ZnPh_2$ with morpholine. $ZnPh_2$ (0.038 g, 0.173 mmol), morpholine (15.1 μL, 0.173 mmol), and 1,3,5-trimethoxybenzene (internal standard) were combined in CD_2Cl_2 (0.5 mL). The homogeneous solution was heated to 50 °C in an oil bath for 15 minutes. ^1H NMR spectroscopic data indicated complete conversion to $PhZn(NC_4H_8O)$. ^1H NMR (CD_2Cl_2): δ 7.64 (d, J = 6.5 Hz, 2H), 7.32 (t, J = 7.0 Hz, 2H), 7.28 (m, 1H), 3.82-3.75 (br, 4H), 3.38-3.28 (br, 4H).

References

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