Photoreduction of Aromatic Ketones in Hexamethylphosphoric Triamide (HMPA): Formation of Stable Coupling Products with HMPA

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Synopsis. Irradiation of aromatic carbonyl compounds in hexamethylphosphoric triamide (HMPA) resulted in the cross-coupling of ketyl radicals with the HMPA-derived radical generated via hydrogen abstraction from it. The results on acetolysis, methanolysis, and the reaction with thionyl chloride of the resulting coupling products are described.

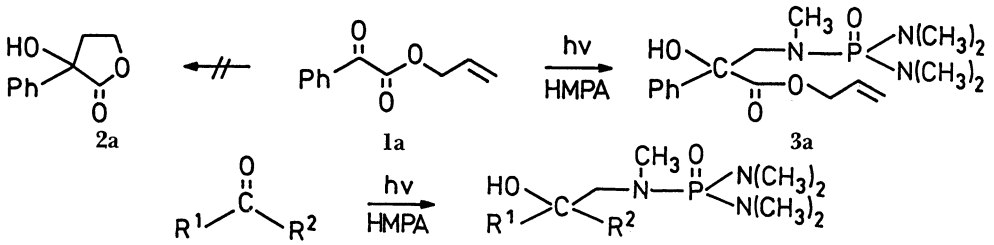
The intermolecular photoreduction of carbonyl compounds by amines is a well investigated reaction.[1] In general, an electron transfer from the amine-nitrogen to the excited carbonyl and successive α-hydrogen abstraction from the amine result in the formation of a ketyl as well as an amine-derived radical. Further steps of the photoreduction are accomplished by various radical combinations.

Recently, the most elegant application of this reaction to natural product synthesis was reported by Cossy et al.,[2] a photoreductive cyclization of δ, ε-unsaturated ketones to cyclopentanols in the presence of triethylamine or HMPA. We originally planned to modify this reaction to prepare α-hydroxylactones from α-ketoesters bearing alkenyl substituents using HMPA as solvent. Instead of intramolecular photoreductive cyclization, we obtained HMPA associated products which were not reported in the former reaction. The formation of cross-coupling products was general when the photolysis of aromatic ketones was carried out in the presence of HMPA. To the best of our knowledge, this is the first trapping of the photochemically generated HMPA radical.

Benzoylformic acid allyl ester (**1a**) in HMPA was irradiated by high pressure mercury lamp in a pyrex test tube. The resulting mixture was directly loaded on silica-gel column (EtOAc). Based on the following spectral data the obtained product (**3a**) was identified as the cross coupling product between the ketyl radical of **1a** and HMPA radical (the radical generated by the α-hydrogen abstraction). The ^{1}H NMR (δ, $CDCl_3$) spectrum of **3a** showed methylene protons at 3.83 (dd, J_{HP}=12.0 Hz, J_{gem}=15.0 Hz) and 3.55 (dd, J_{HP}=11.4 Hz and J_{gem}=15.0 Hz), and one methyl group at δ=2.41 (d, J_{HP}=8.8 Hz) as well as three equivalent methyl groups at 2.59 (d, J_{HP}=9.6 Hz) and 2.63 (d, J_{HP}=9.6 Hz), respectively. The ^{13}C NMR spectrum of **3a** also showed the presence of phosphorus atom since $^2J_{CP}$ was observed for C-2 (J=4.9 Hz). Keto ester (**1b**) also reacted with HMPA under irradiation to give **3b**.

In the former case, no reductive cyclization product (**2a**) was obtained. The distinctive difference between Cossy's system[2] and the present one might be the stability difference of the ketyl radicals formed. The ketyl radicals derived from **1a** and **1b** are more stable than the former one due to the stabilization by ester and phenyl groups, which reduces the reactivity of the radicals. The formation of HMPA associated products was unprecedented in photoreduction of carbonyl compounds.

To survey the general behavior of ketones to HMPA under photolytic conditions, a variety of ketones was examined. Aromatic ketones (**1c—h**) afforded cross-coupling products (**3c—h**) in overall yields of 31—



	R_1	R_2
a	Ph	$COOCH{=}CH_2$
b	Ph	$COCH_3$
c	Ph	4-CH_3-C_6H_4
d	Ph	CH_3
e	Ph	Ph
f	4-CH_3-C_6H_4	4-CH_3-C_6H_4
g	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4
h	Fluorenylidene	

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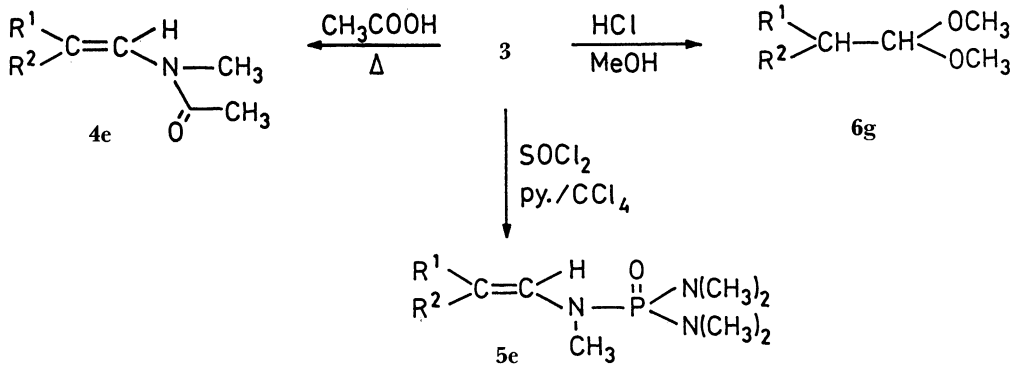
Table 1. Formation of Cross-Coupling Products **3** between Carbonyl Compounds **1** and HMPA by Irradiation

Entry	1	R^1	R^2	Molar ratio HMPA/1	Irradn. time/h	Yield/% 3	Yield/% pinacol	Conversion %
1	**1a**	Ph	$COOCH=CH_2$	50	5	20	—[a]	44
2				5.3	4	7	—[a]	8
3	**1b**	Ph	$COCH_3$	4.5	4	13	26[b]	100
4	**1c**	Ph	4-CH_3-C_6H_4	6.5	4	31	22	100
5				4.8	20	55	29	100
6	**1d**	Ph	CH_3	3.6	5	14	27	75
7				2.8	22	38	13	100
8	**1e**	Ph	Ph	5.5	6	24	9	39
9				3.4	60	40	33	100
10	**1f**	4-CH_3-C_6H_4	4-CH_3-C_6H_4	5.6	9	41	—[a]	55
11	**1g**	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	5.6	44	64	16	94
12	**1h**	Fluorenylidene		4.0	32	44	13	80

a) Not determined. b) Two diastereomeric pinacols had been obtained.



64%. The results are summarized in Table 1. The only isolated by-products were the corresponding pinacols. To ensure the type of phosphorus atom involved in the coupling products, ^{31}P NMR spectra of **5c** and **5e** were taken. In both cases, one signal at $\delta=-30.2$ (downfield from external 85% H_3PO_4) was observed and its chemical shift was very close to that of HMPA, $\delta=-26.3$ (lit, −23.4 ppm).[3] No reaction was observed for an aliphatic keto ester (R^1=Me, $R^2=COOCH_2$-CH=CH_2), aliphatic ketones, ($R^1=R^2$= Me; R^1=Me; R^2=CH=CH_2, Et), as well as for some aromatic ketones (R^1=Ph; $R^2=CH_2COMe$, CH=CHPh, CH_2N, CH(OH)Ph).

Compound **3** proved to be stable to bases (10 M NaOH, 30 °C; *n*-BuLi, r.t.), but reacted easily with acids. The reaction of **3e** with refluxing acetic acid led to the enamide (**4**). Treatment of **3e** with thionyl chloride in CCl_4/pyridine gave the olefin without cleavage of the P-N bond in 64% yield. Methanolysis of **3g** afforded dimethyl acetal (**6**).

Except an amidation of carboxylic acids by HMPA,[4] its use as a reagent is quite limited. Generally, it is assumed to be an inert solvent though it can form complexes with alcohols, phenols, unsaturated carbons,[5] and carboxylic acids.[5,6] The present findings are one of the rare examples of the derivatization of HMPA.

Experimental

Melting points were uncorrected. The ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ with tetramethylsilane as an internal standard, on a JEOL GSX 500 and a JEOL FX 270 spectrometers, respectively. Mass spectra were measured with a HITACHI RMU-7M spectrometer at 70 eV of ionization energy. Elemental analyses were obtained with a Perkin-Elmer-240. IR spectra were recorded on a JASCO A-202 infrared spectrophotometer.

HMPA was distilled from CaH_2 and stored over molecular sieves (4A). FUJIGEL BW 200 was used for column chromatography. Compounds were purified by HPLC using a HITACHI L-4000/L-6050 system with LiChrosorb Si 60 column (10×250 mm). Photoreactions were carried out using a 400 W high pressure mercury lamp (USHIO UM-452).

Photoreactions of Carbonyl Compounds 1. A General Procedure. The solution of **1** (1—2 mmol) in HMPA (3—50 equiv to **1**) was degassed by bubbling of argon for 10 min prior to irradiation. After irradiation (externally in a pyrex test tube under cooling with water) the resulting HMPA solution was chromatographed on silica gel with ethyl acetate as eluent. The reaction products were thus isolated and purified by HPLC.

Cross-Coupling Products (3a—h).

3a: IR (neat) 3200, 2900, 1725, 1160; ^1H NMR $\delta=7.71$ (m, 2H), 7.31 (m, 4H, 1H was exchanged with D_2O), 5.87 (dddd, J=13.0, 11.9, 5.8, 5.5 Hz, 1H), 5.23 (ddd, J=17.3, 1.4, 1.4 Hz, 1H), 5.16 (ddd, J=11.9, 1.4, 1.4 Hz, 1H), 4.67 (dddd, J=13.0, 5.8, 1.4, 1.4, 2H), 4.60 (dddd, J=13.0, 5.5, 1.4, 1.4 Hz), 3.83 (dd, J_{HP}=12.0 and J=15.0 Hz, 1H), 3.55 (dd, J_{HP}=11.4 and J=15.0 Hz, 1H), 2.62 (d, J_{HP}=9.6 Hz, 12H), 2.41 (d, J_{HP}=8.8 Hz, 3H); ^{13}C NMR $\delta=173.7$ (s), 141.1 (s), 131.9 (d), 128.1 (d), 127.6 (d), 125.8 (d), 118.5 (t), 78.6 (s), 65.9 (t), 59.5 (td, J_{CP}=4.9 Hz), 37.7 (qd, J_{CP}=2.9 Hz), 36.7 (qd, J_{CP}=3.9, Hz), 36.6 (qd, J_{CP}=4.9 Hz); Found: *m/z* 370.1900; Calcd for $C_{17}H_{29}N_3O_4P$:

MH^+, 370.1894.

3b: IR (neat) 3350, 2900, 1720, 1160; ^{1}H NMR δ=7.71 (m, 2H), 7.32 (m, 4H, 1H was exchanged with D_2O), 3.83 (dd, J_{HP}=12.0 Hz and J=15.0 Hz, 1H), 3.73 (s, 3H), 3.55 (dd, J_{HP}=11.5 Hz and J=15.0 Hz, 1H), 2.64 (d, J_{HP}=9.6 Hz, 6H), 2.59 (d, J_{HP}=9.6 Hz, 6H), 2.40 (d, J_{HP}=9.1 Hz, 3H); ^{13}C NMR δ=173.7 (s), 141.1 (s), 128.1 (d), 127.6 (d), 125.7 (d), 78.6 (s), 59.4 (td, J_{CP}=5.9 Hz), 52.6 (q), 37.6 (qd, J_{CP}=3.0 Hz), 36.64 (qd, J_{CP}=4.4 Hz), 36.58 (qd, J_{CP}=5.9 Hz); Found: *m/z* 284.1553; Calcd for $C_{13}H_{23}N_3O_2P$: $M^+-C_2H_3O_2$, 284.1526.

3c: Mp 127—132 °C (ethyl acetate); IR ($CHCl_3$) 3350, 1160; ^{1}H NMR δ=7.54 (m, 2H), 7.42 (m, 2H), 7.28 (m, 2H), 7.19 (m, 1H), 7.09 (m, 2H), 6.93 (s, 1H, exchanged with D_2O), 3.84 (m, J_{HP}=11.3 Hz and J=14.7 Hz, 2H), 2.62 (d, J_{HP}=9.6 Hz, 6H), 2.60 (d, J_{HP}=9.6 Hz, 6H), 2.30 (s, 3H), 2.06 (d, J_{HP}=8.8 Hz, 3H); ^{13}C NMR δ=146.9 (s), 143.8 (s), 136.0 (s), 128.5 (d), 127.7 (d), 126.7 (d), 126.5 (d), 126.4 (d), 76.5 (s), 60.6 (td, J_{CP}=4.9 Hz), 37.6 (qd, J_{CP}=3.9 Hz), 36.7 (qd, J_{CP}=3.9 Hz), 21.0 (q).; MS *m/z* (rel intensity) 375 (M^+, 1), 357 (2), 179 (65), 135 (100); Found: C, 63.75; H, 7.86; N, 11.14%; Calcd for $C_{20}H_{30}N_3O_2P$: C, 63.97; H, 8.07; N, 11.19%.

3d: Mp 81—83 °C (ethyl acetate); IR ($CHCl_3$) 3250, 1160; ^{1}H NMR 7.57 (m, 2H), 7.26 (m, 3H), 6.58 (s, 1H, exchanged with D_2O), 3.44 (dd, J_{HP}=10.0 Hz and J=15.0 Hz, 1H), 3.11 (dd, J_{HP}=13.2 Hz and J=15.0 Hz, 1H), 2.62 (d, J_{HP}=9.6 Hz, 6H), 2:60 (d, J_{HP}=9.6 Hz, 6H), 2.21 (d, J_{HP}=9.1 Hz, 3H), 1.53 (s, 3H); ^{13}C NMR δ=147.5 (s), 127.8 (d), 126.3 (d), 125.8 (d), 74.0 (s), 62.4 (td, J_{CP}=4.4 Hz), 37.9 (qd, J_{CP}=4.4 Hz), 36.7 (qd, J_{CP}=4.4 Hz), 36.6 (qd, J_{CP}=4.4 Hz), 28.0 (q); MS *m/z* (rel intensity) 229 (M^+, 0.3), 281 (0.8), 179 (48), 135 (100); Found: C, 56.30, H, 8.61, N, 13.83%; Calcd for $C_{14}H_{26}N_3O_2P$: C, 56.16, H, 8.77, N, 14.04%.

3e: Mp 141—143 °C (ethyl acetate); IR ($CHCl_3$) 3250, 1160; ^{1}H NMR δ=7.55 (m, 4H), 7.28 (m, 4H), 7.20 (m, 2H), 7.02 (s, 1H, exchanged with D_2O), 3.86 (d, J_{HP}=11.5 Hz, 2H), 2.61 (d, J_{HP}=9.6 Hz, 12H), 2.06 (d, J_{HP}=9.1 Hz, 3H); ^{13}C NMR δ=146.7 (s), 127.8 (d), 126.7 (d), 126.5 (d), 77.6 (s, observed in $(CD_3)CO$), 60.6 (td, J_{CP}=4.9 Hz), 37.7 (qd, J_{CP}=3.9 Hz), 36.7 (qd, J_{CP}=3.9 Hz); MS *m/z* (rel intensity) 361 (M^+, 0.6), 343 (4), 179 (100), 135 (100); Found: C, 63.19; H, 7.81; N, 11.62%; Calcd for $C_{19}H_{28}N_3O_2P$: C, 63.13; H, 7.82; N, 11.63%.

3f: Mp 164—167 °C (ethyl acetate); IR ($CHCl_3$) 3250, 2950, 2900, 1150; ^{1}H NMR δ=7.41 (d, J=8.3 Hz, 4H), 7.08(d, J=8.3 Hz, 4H), 6.84 (s, 1H, exchanged with D_2O), 3.82 (d, J_{HP}=11.3 Hz, 2H), 2.61 (d, J_{HP}=9.4 Hz, 12H), 2.30 (s, 6H), 2.07 (d, J_{HP}=9.1 Hz, 3H); ^{13}C NMR δ=144.0 (s), 135.9 (s) , 128.4 (d) , 126.5 (d), 76.4 (s), 60.6 (td, J_{CP}=5.9 Hz), 37.6 (qd, J_{CP}=3.9 Hz), 36.7 (qd, J_{CP}=3.9 Hz), 21.0 (q); MS *m/z* (rel intensity) 389 (M^+, 1), 371 (3), 179 (67), 135 (100); Found: C, 64.38; H, 8.25; N, 10.47%; Calcd for $C_{21}H_{32}N_3O_2P$: C, 64.75; H, 8.30; N, 10.79%.

3g: Mp 139—142 °C (ethyl acetate); IR ($CHCl_3$) 3250, 2850, 1160; ^{1}H NMR δ=7.44 (m, 4H), 6.89 (s, 1H, exchanged with D_2O), 6.83 (m, 4H), 3.78 (s, 6H), 3.78 (d, J_{HP}=11.3 Hz, 2H), 2.62 (d, J_{HP}=9.6 Hz, 12H), 2.09 (d, J_{HP}=9.1 Hz, 3H); ^{13}C NMR δ=158.2 (s), 139.2 (s), 127.8 (s), 113.1 (s), 76.2 (s), 60.8 (td, J_{CP}=5.9 Hz), 55.2 (q), 37.7 (qd, J_{CP}=2.9 Hz), 36.7 (qd, J_{CP}=3.9 Hz); MS *m/z* (rel intensity) 421 (M^+, 2), 403 (12), 179 (58), 135 (100); Found: C, 59.74: H, 7.61; N, 9.95%; Calcd for $C_{21}H_{32}N_3O_4P$: C, 59.83; H, 7.67; N, 9.97%.

3h: Mp 184—186 °C (ethyl acetate); IR ($CHCl_3$) 3200, 2960, 1180; ^{1}H NMR δ=7.62 (m, 4H), 7.30 (m, 5H, 1H was exchanged with D_2O), 3.33 (d, J_{HP}=11.6 Hz, 2H), 2.74 (d, J_{HP}=9.4 Hz, 12H), 2.42 (d, J_{HP}=9.1 Hz, 3H); ^{13}C NMR δ=148.9 (s), 139.2 (s), 128.4 (d), 127.4 (d), 124.5 (d), 119.8 (d), 81.8 (s), 60.7 (td, J_{CP}=4.9 Hz), 38.4 (qd, J_{CP}=2.9 Hz), 36.8 (qd, J_{cP}=3.9 Hz); MS *m/z* (rel intensity) 359 (M^+, 0.7), 341 (3), 179 (56), 135 (100); Found: C, 63.49; H, 7.26; N, 11.73%; Calcd for $C_{19}H_{26}N_3O_2P$: C, 63.48; H, 7.31, N, 11.69%.

Acetamid 4e: A solution of **3e** (200 mg, 0.55 mmol) in acetic acid (5 ml) was refluxed for 4h. After complete disappearance of the starting material, acetic acid was removed in vacuo. The residual oil was dissolved in ethyl acetate and chromatographed on silica gel (ethyl acetate : hexane=1 : 1), yielding 104 mg (75%) of **4e**: Mp 79—82 °C (hexane-ethyl acetate); IR ($CHCl_3$) 3000, 1655, 1610; ^{1}H NMR δ=7.38—7.17 (m, 10H), 6.72 (s, 1H), 2.76 (s, 3H), 2.13 (s, 3H); ^{13}C NMR δ=171.0 (s), 148.0 (s), 138.2 (s), 135.9 (s),129.8 (d), 128.6 (d), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 35.1 (q), 22.6 (q); MS *m/z* (rel intensity) 251 (M^+, 77), 209 (100), 193 (32); Found: C, 80.98; H, 6.81; N, 5.44%; Calcd for $C_{17}H_{17}NO$: C, 81.23; H, 6.83; N, 5.57.

Phosphoric Triamide 5e: To a stirred solution of **3e** (200 mg, 0.55 mmol) and pyridine (0.05 ml, 0.6 mmol) in dry carbon tetrachloride (10 ml), thionyl chloride (0.07 ml, 1.0 mmol) was slowly added at room temperature. The resulting suspension was stirred for additional 30 min. After addition of water, the organic layer was separated, washed two times with water and dried over anhydrous $MgSO_4$. Carbon tetrachloride was removed in vacuo and the residue was chromatographed on silica gel (ethyl acetate) to give 112 mg (59%) of **5e**: IR (neat) 2900, 1610; ^{1}H NMR δ=7.10—7.40 (m, 10H), 6.75 (d, J_{HP}=6.3 Hz, 1H), 2.71 (d, J_{HP}=9.6 Hz, 12H), 2.48 (d, J_{HP}=8.8 Hz, 3H); ^{13}C NMR δ=131.1 (d), 130.85 (s), 130.79 (d), 128.12 (d), 128.10 (d), 128.0 (d), 127.3 (d), 126.9 (d), 126.0 (d), 36.8 (qd, J_{CP}=3.8 Hz), 35.9 (qd, J_{CP}=3.1 Hz); MS *m/z*, (rel intensity) 343 (M^+, 29), 165 (26), 135 (82), 105 (100); Found: C, 66.24; H, 7.35; N, 12.24%; Calcd for $C_{19}H_{26}NOP$: C, 66.44; H, 7.65; N, 12.24%.

Dimethyl Acetal 6g: A solution of **3g** (200 mg, 0.47 mmol) in 2 M (M=mol dm^{-3}) HCl (3 ml) and methanol (10 ml) was heated upto 40 °C. The solution was left to stand overnight at this temperature. After evaporation of solvent (at 40 °C), the residue was diluted with 20 ml of water and then extracted with dichloromethane (20 ml×3). The combined extract was dried over anhydrous $MgSO_4$. The resulting residue after removal of solvent in vacuo was chromatographed on silica-gel to afford 25 mg (18%) of acetal **6g**: Mp 61—65 °C (hexane-ethyl acetate, 1 : 1); IR ($CHCl_3$) 2950, 1600; ^{1}H NMR δ=7.20 (d, J=8.5 Hz, 4H), 6.82 (d, J=8.5 Hz, 4H), 4.80 (d, J=7.4 Hz, 1H) , 4. 13 (d, J=7.4 Hz, 1H) , 3.76 (s, 6H), 3.30 (s, 6H); ^{13}C NMR 158.1 (s), 133.6 (s), 129.6 (d), 113.7 (d), 106.9 (d), 55.2 (q), 54.1 (q), 52.8 (d); Found: C, 71.53; H, 7.22%: Calcd for $C_{18}H_{22}O_4$: C, 71.49; H, 7.35%.

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