C-Alkylation of Tosyl- and 2,4-Dinitrophenylhydrazones through an *in Situ* Sequence under Phase-Transfer Conditions

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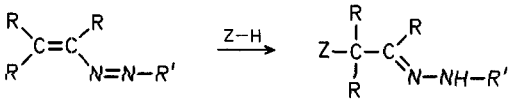
Azoalkenes with[1,2] or without[3] an electron-withdrawing group on the "terminal" nitrogen are known to undergo a 1,4-conjugate addition to give a *C*-functionalization which may be of great utility in synthetic applications (Scheme A).



Scheme A

However, azoalkenes as intermediates are not always easily available. On the contrary, often they are (see tosylazoalkenes[4]) particularly unstable intermediates, very difficult to preserve, and to purify. Thus, it may be useful to realize their *in situ* synthesis and utilization from suitable precursors. In a previous paper[2], we reported an *in situ* sequence which allows the α-methylation (phenylation) and α,α'-dimethylation (diphenylation) of tosylhydrazones through the formation of tosylazoalkene intermediates.

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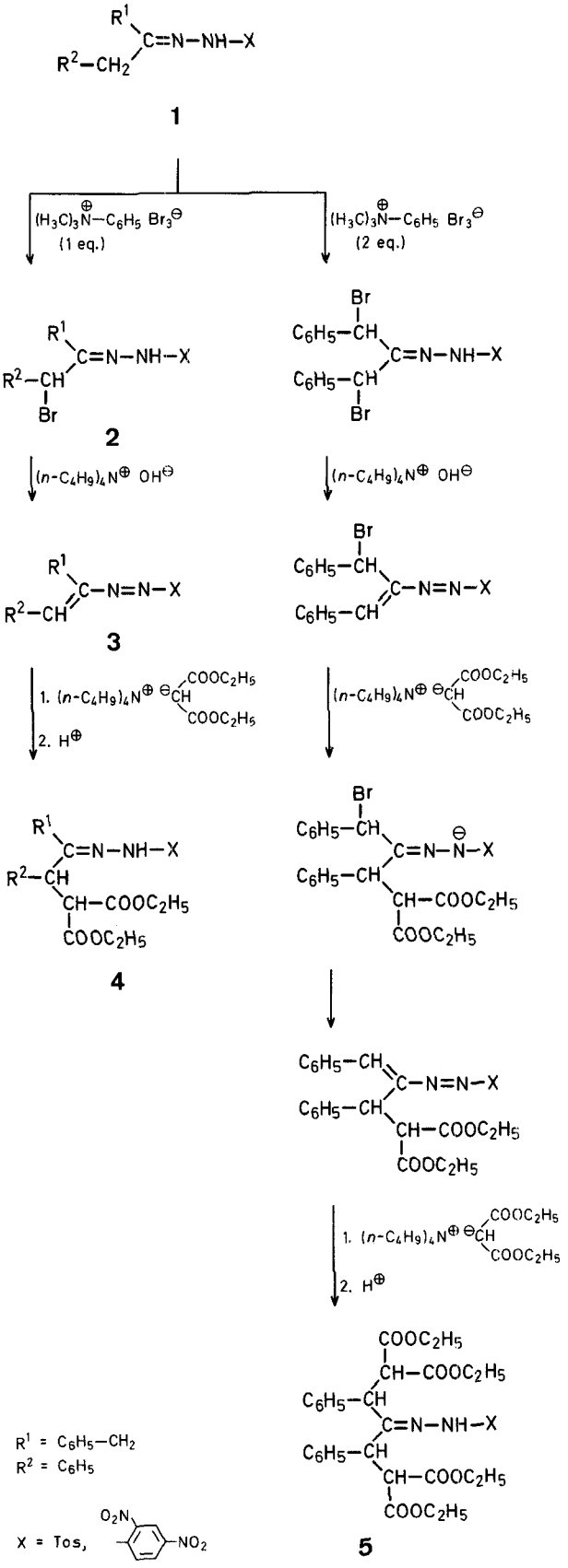
Now we report an extension of this methodology to phase-transfer conditions. In this case, the *C*-alkylation of hydrazonic systems (tosyl- and 2,4-dinitrophenylhydrazones) is effected with a resonance-stabilized carbanion such as that of ethyl malonate according to Scheme **B** (left hand side).



Scheme **B**

The tetrahydrofuran solution of the brominated *N*-substituted hydrazone[5] is added to the dichloromethane solution of the nucleophile, prepared from solid finely triturated sodium hydroxide, tetrabutylammonium hydrogen sulfate, and diethyl malonate. The reaction mixture is maintained with stirring at room temperature for 15–30 min and then worked-up. Pure *C*-alkylated products **4** were obtained in satisfactory overall yields through chromatographic separation on a silica gel column.

As previously reported[2], this methodology is also convenient for α,α'-difunctionalization. Thus, α,α'-dialkylation of tosyl- and 2,4-dinitrophenylhydrazones was carried out (see entry **5a** and **5b** in the Table) under the above conditions simply by varying the molar ratios of the reagents, presumably according to Scheme **B** (right hand side).

It must be emphasized that the success of this method is essentially dependent on the course of the bromination step and on the stability of the azoalkene intermediate. Thus, we obtained poor results when loss in bromination selectivity was observed and/or when no resonance-stabilized azoalkenes were present along the reaction pathway[6].

C-Alkylation of tosyl- and 2,4-dinitrophenylhydrazones was also carried out under liquid-liquid two-phase conditions, by adding the dichloromethane solution of the brominated *N*-substituted hydrazone to a basic aqueous solution containing the nucleophile and the phase-transfer catalyst. However, under these conditions, lower yields were obtained as a result of the known instability of azoalkene systems in the presence of protic media[7]. As expected, by using tosylhydrazones as starting materials, less satisfactory results were obtained[8].

Melting points are uncorrected and were determined with a Büchi apparatus. The starting hydrazones were prepared from the corresponding commercially available ketones using standard methods. Tetrabutylammonium hydrogen sulfate and phenyltrimethylammonium tribromide were purchased from Fluka and were used as received. Analytical T.L.C. was carried out on pre-coated plates of Silica Gel F_{254} (0.25 mm; Merck). The reaction products were purified on Silica Gel (Merck, 230–400 mesh) columns, eluting with cyclohexane/ethyl acetate mixtures. All the reported reactions were carried out on a 2.5–3.0 mmol scale using 0.01–0.015 molar tetrahydrofuran solutions of the starting hydrazone.

Monoalkylation of Dibenzyl Ketone 2,4-Dinitrophenylhydrazone with Diethyl Malonate:

To a tetrahydrofuran solution (200 ml) of dibenzyl ketone 2,4-dinitrophenylhydrazone (1.0 g, 2.56 mmol) is added phenyltrimethylammonium tribromide (1.06 g, 2.82 mmol) in portions at room temperature with stirring. The bromination is followed by T.L.C. The mixture containing the brominated hydrazone is added at room temperature with stirring to a suspension prepared from tetrabutylammonium hydrogen sulfate (1.83 g, 5.38 mmol), finely triturated solid sodium hydroxide (2.05 g, 51.2 mmol), diethyl malonate (0.82 g, 5.12 mmol), and dichloromethane (150 ml). After 0.25 h, the reaction mixture is poured into a 2 normal hydrogen chloride solution, washed with water, the organic layer separated, and dried with sodium sulfate. The solvent is removed under reduced pressure to leave a residue from which pure **4b** is obtained by chromatography on Silica Gel, eluting with *n*-hexane/ethyl acetate 75/25; yield: 0.985 g (70%).

Dialkylation of Dibenzyl Ketone 2,4-Dinitrophenylhydrazone with Diethyl Malonate:

Carried out as described above using doubled amounts of phenyltrimethylammonium tribromide, sodium hydroxide, and diethyl malonate. Pure **5b** is obtained after chromatographic separation on Silica Gel column eluting with 80/20 cyclohexane/ethyl acetate; yield: 0.182 g (10%).

Table. *C*-Alkylation of Tosyl- and 2,4-Dinitrophenylhydrazones[a]

Substrate No.	R^1	R^2	X	m.p. (Lit. m.p.)	Product	Yield [%][b]	m.p.	Molecular formula[c]	I.R. (nujol)[d] $\nu_{C=O}$ [cm^{-1}]	M.S. (70 eV)[e] *m/e* (relative intensity)
1a	$C_6H_5CH_2$	C_6H_5	Tos	175–177 °C (175–177 °C)[4]	**4a**	55	131–132 °C	$C_{29}H_{32}N_2O_6S$ (536.6)	1750	536 (M^+, 0.4); 491 (M−45, 0.9); 381 (M−155, 7); 335 (M−46−155, 4); 91 (100)
1b	$C_6H_5CH_2$	C_6H_5	2,4-Dnp	97–99 °C (98.5–99.5 °C)[9]	**4b**	70	129 °C	$C_{28}H_{28}N_4O_8$ (548.5)	1730	548 (M^+, 21); 503 (M−45, 5); 91 (100)
1c	C_6H_5	C_6H_5	Tos	135–137 °C (135–137 °C)[4]	**4c**	51	154–155 °C	$C_{28}H_{30}N_2O_6S$ (522.6)	1745, 1725	522 (M^+, 18); 477 (M−45, 11); 367 (M−155, 57); 321 (M−155−46, 17); 191 (100)
1d	C_6H_5	C_6H_5	2,4-Dnp	197–198 °C (198–199 °C)[10]	**4d**	35	134–136 °C	$C_{27}H_{26}N_4O_8$ (534.5)	1750	534 (M^+, 2); 489 (M−45, 2); 103 (100)
1e	H_3C	C_6H_5	Tos	133–135 °C (133–134 °C)[11]	**4e**	42	141–143 °C	$C_{23}H_{28}N_2O_6S$ (460.5)	1725	460 (M^+, 5); 415 (M−45, 11); 305 (M−155, 43); 260 (M−155−45, 11); 91 (100)
1f	H_3C	C_6H_5	2,4-Dnp	153–155 °C (154–155 °C)[12]	**4f**	52	120–121 °C	$C_{22}H_{24}N_4O_8$ (472.4)	1730, 1715	472 (M^+, 5); 427 (M−45, 2), 30 (100)
1g			2,4-Dnp	254–256 °C (256–257 °C)[13]	**4g**	23	128–130 °C	$C_{23}H_{24}N_4O_8$ (484.5)	1735	484 (M^+, 20); 439 (M−45, 11); 210 (100)
1a	$C_6H_5CH_2$	C_6H_5	Tos	—	**5a**	18	131–133 °C	$C_{36}H_{42}N_2O_{10}S$ (694.8)	1755	694 (M^+, 6); 649 (M−45, 9); 648 (M−46, 6), 539 (M−155, 100); 493 (M−46−155, 46)
1b	$C_6H_5CH_2$	C_6H_5	2,4-Dnp	—	**5b**	10	119–121 °C	$C_{35}H_{38}N_4O_{12}$ (706.7)	1750, 1740	706 (M^+, 0.1); 661 (M−45, 0.4); 660 (M−46, 0.3); 132 (100)

[a] The ^{1}H-N.M.R. spectra of all products are in accord with the proposed structures; the C_2H_5 protons of the ethyl malonate moiety are not magnetically equivalent. For the —CH—CH(COOCH$_2$—)$_2$ system protons for products **4** $\delta = 3.0$–4.7 (6H) and for products **5** $\delta = 3.2$–5.2 ppm (12H). For the methyl groups $\delta = 0.7$–1.4 ppm (*t*).

[b] Yield of pure, isolated product based on **1**.

[c] The microanalyses were in satisfactory agreement with the calculated values (C ±0.31, H ±0.20, N ±0.23).

[d] Recorded with a Perkin-Elmer 337 grating spectrophotometer.

[e] Measured with a Hewlett-Packard MS 5980 A spectrometer.

Dedicated to Professor L. Panizzi on the occasion of his 70th birthday.

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[6] With 4-heptanone and cyclohexanone tosylhydrazones as starting materials, complex reaction mixtures were obtained. Even the tetralone tosylhydrazone, which may be the precursor of a cross-conjugated azoalkene did not give good results.

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[8] As an example, the C-alkylated derivative was obtained in 35% and 65% yield starting from dibenzyl ketone tosyl- and 2,4-dinitrophenylhydrazone, respectively.

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