Preparation of Aryldiazoalkanes from 2,4,6-Triisopropylbenzenesulphonyl Hydrazones

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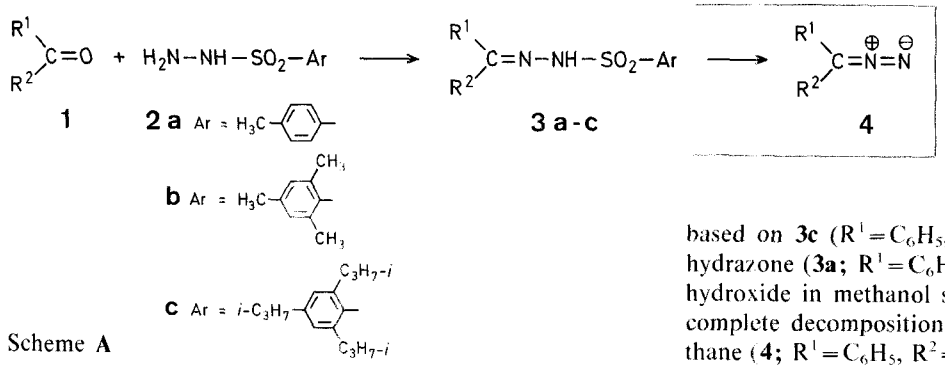
The Bamford-Stevens reaction[1] is the key step in a convenient procedure for the conversion of aldehydes and ketones into the corresponding diazoalkanes. The aldehyde or ketone **(1)** is first treated (Scheme A) with tosyl hydrazide **(2a)** and the resulting tosyl hydrazone[1] **(3a)** is usually then heated with alkoxide ion in a suitable solvent to give the desired diazoalkane **(4)** or a decomposition product or a derivative thereof. While the latter conditions are to some extent satisfactory (see below) for the preparation of the relatively stable aryldiazoalkanes (**4**; R^1 = aryl, R^2 = H, alkyl or aryl), it is necessary in the case of aliphatic or alicyclic diazoalkanes (**4**; R^1, R^2 ≠ aryl) to preform a salt of the tosyl hydrazone **(3a)** and then to heat it in vacuo[2].



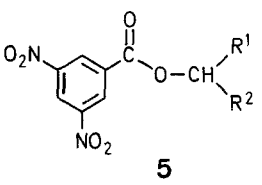
Scheme A

In their original studies, Bamford and Stevens showed[1] that when benzaldehyde tosylhydrazone (**3a**; $R^1 = C_6H_5$, $R^2 = H$) is heated with sodium ethoxide in ethanol solution for 6 h at 50°C, phenyldiazomethane (**4**; $R^1 = C_6H_5$, $R^2 = H$) is obtained in ~62% yield. Farnum later showed[3] that when **3a** ($R^1 = C_6H_5$, $R^2 = H$) is heated with a stoichiometric quantity of dry sodium methoxide in pyridine solution at 60°C for 30 min, phenyldiazomethane is obtained in 65–70% yield, as estimated by the quantity of nitrogen evolved on decomposition. Other aryldiazoalkanes are obtained, albeit in somewhat lower yields, by the same procedure. Polish workers[4] have more recently prepared a number of aryldiazoalkanes (**4**; R^1 = aryl, R^2 = H, alkyl or aryl) by heating dioxan or diglyme solutions of the corresponding tosyl hydrazones **(3a)** with 50% aqueous sodium hydroxide at 80–105°C for 1–2.5 h. Insofar as it is possible to make a comparison, the yields obtained by the latter procedure[4] correspond approximately to those reported by Farnum[3].

It is clear from Bamford and Stevens' and more especially from Farnum's studies[1,3] that, at a given temperature, there are optimum reaction times for the preparation of aryldiazoalkanes (**4**; R^1 = aryl). Indeed, it is apparent that aryldiazoalkanes are unstable under the conditions required to decompose their tosyl hydrazone precursors (**3a**; R^1 = aryl). Several years ago, we originally reported[5] that 2,4,6-triisopropylbenzenesulphonyl hydrazide **(2c)** and mesitylene-2-sulphonyl hydrazide **(2b)** undergo base-catalysed decomposition in deuteriomethanol solution at, respectively, ~380 and ~16 times the rate of tosyl hydrazide **(2a)**. We attributed[5] this rate enhancement to the greater release of steric compression in arenesulphonyl hydrazides with bulky *ortho*-substituents and later exploited it in the development both of a convenient nitrile synthesis[6] and a modification[7] of the McFadyen-Stevens reaction[8]. We also demonstrated[9] that mesitylene-2-sulphonyl hydrazide **(2b)** is a superior reagent to tosyl hydrazide **(2a)** in the Eschenmoser fragmentation reaction[10].

We now report that 2,4,6-triisopropylbenzenesulphonyl hydrazones (**3c**; R^1 = aryl) are more satisfactory intermediates than the corresponding tosyl hydrazones (**3a**; R^1 = aryl) in the preparation of aryldiazoalkanes. [It was previously reported[11] that the 2,4,6-triisopropylbenzenesulphonyl hydrazone derived from camphor is much more rapidly converted into tricyclane than the corresponding tosyl hydrazone.]

The required intermediate 2,4,6-triisopropylbenzenesulphonyl hydrazones[5] **(3c)** are readily prepared in high yields (Table 1) by treating the corresponding aldehydes and ketones **1** with 1.1 molar equivalents of **2c** in methanol solution. A catalytic quantity of concentrated hydrochloric acid is added in the reactions involving ketones (Table 1, entries 2, 3, 6, and 7). When benzaldehyde 2,4,6-triisopropylbenzenesulphonyl hydrazone (**3c**; $R^1 = C_6H_5$, $R^2 = H$) is heated with 2 molar equivalents of potassium hydroxide in methanol solution, under reflux (Table 2, entry 1), it undergoes complete decomposition in 7 min to give phenyldiazomethane (**4**; $R^1 = C_6H_5$, $R^2 = H$). When the crude product is treated with a twofold excess of 3,5-dinitrobenzoic acid in tetrahydrofuran, benzyl 3,5-dinitrobenzoate (**5**; $R^1 = H$, $R^2 = C_6H_5$) is obtained[12] in 90% yield,



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based on **3c** ($R^1 = C_6H_5$, $R^2 = H$). When benzaldehyde tosyl hydrazone (**3a**; $R^1 = C_6H_5$, $R^2 = H$) is treated with potassium hydroxide in methanol solution under the same conditions, complete decomposition takes 21 h and no phenyldiazomethane (**4**; $R^1 = C_6H_5$, $R^2 = H$) is then detected. However, benzyl methyl ether may be isolated from the products in 45% yield. Under the same conditions, decomposition of benzaldehyde mesitylene-2-sulphonyl hydrazone (**3b**; $R^1 = C_6H_5$, $R^2 = H$) is complete in 75 min, but treatment of the phenyldiazomethane obtained with an excess of 3,5-dinitrobenzoic acid gives benzyl 3,5-dinitrobenzoate (**5**; $R^1 = H$, $R^2 = C_6H_5$) in only 57% isolated yield.

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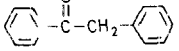
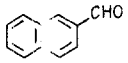
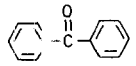
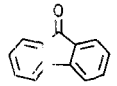
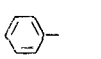
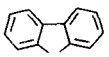
The corresponding diazoalkanes are also rapidly obtained and in very satisfactory yields by heating the 2,4,6-triisopropylbenzenesulphonyl hydrazones of deoxybenzoin, 2-nitrobenzaldehyde, 2-naphthaldehyde, benzophenone, and fluorenone (Table 2, entries 3, 4, 5, 6, and 7, respectively) with 2 molar equivalents of potassium hydroxide in boiling methanol solution. It is noteworthy that the decomposition of the 2,4,6-triisopropylbenzenesulphonyl hydrazone of acetophenone (entry 2) proceeds much more slowly than the decomposition of the corresponding deoxybenzoin derivative (entry 3) under the same conditions, and gives **4** ($R^1 = C_6H_5$, $R^2 = CH_3$) [as estimated from the yield of the isolated 3,5-dinitrobenzoate ester (**5**; $R^1 = C_6H_5$, $R^2 = CH_3$)] only in modest yield. Acetophenone azine (26%) is also obtained[1]. Perhaps the most surprising result of all is that, although the 2,4,6-triisopropylbenzenesulphonyl hydrazone of pyridine-4-carboxaldehyde (entry 8) reacts with potassium hydroxide in boiling methanol solution very rapidly, none of the corresponding diazoalkane (**4**; $R^1 = C_5H_4N$, $R^2 = H$) is detected in the products. 4-Methoxymethylpyridine (57%) is the sole isolated product.

Table 1. Preparation of 2,4,6-Triisopropylbenzenesulfonyl Hydrazones **3c**

Entry	Hydrazone of	Procedure[a]	Yield [%]	m.p. [°C]	Molecular Formula[b]
1		A	92	188–189°	$C_{22}H_{30}N_2O_2S$ (386.6)
2		B	90	172–173°	$C_{23}H_{32}N_2O_2S$ (400.6)
3		B	95	150–151°	$C_{29}H_{36}N_2O_2S$ (476.7)
4		A	95	169–170°	$C_{22}H_{29}N_3O_4S$ (431.6)
5		A	88	169–170°	$C_{26}H_{32}N_2O_2S$ (436.6)
6		B	92	148–149°	$C_{28}H_{34}N_2O_2S$ (462.7)
7		B	90	203–205°	$C_{28}H_{32}N_2O_2S$ (460.6)

[a] See Experimental for description of procedures A and B.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.22, N ±0.26.

Table 2. Preparation of Aryldiazoalkanes **4** (R^1 = aryl) or Derivatives **5**

Entry	R^1	R^2	Reaction Time [min]	Yield [%] of **4**	Yield [%] of **5**[a]	m.p. [°C]	Molecular Formula[b]
1		H	7	—	90	114–115°	$C_{14}H_{10}N_2O_6$ (302.2)
2		CH_3	110	—	38[c]	98°	$C_{15}H_{12}N_2O_6$ (316.3)
3		$-CH_2-C_6H_5$	10	—	90	192–193°	$C_{21}H_{16}N_2O_6$ (392.4)
4		H	< 5	—	98	142–143°	$C_{14}H_9N_3O_8$ (347.2)
5		H	15	—	65	150–151°	$C_{18}H_{12}N_2O_6$ (352.3)
6			5	—	83	143–144°	$C_{20}H_{14}N_2O_6$ (378.3)
7			< 5	98	—	100–101°	$C_{13}H_8N_2$ (192.2)
8		H	5	0[d]	—	—	

[a] Derivative **5** obtained by treating crude **4** with an excess of 3,5-dinitrobenzoic acid.
[b] Satisfactory microanalyses obtained: C ±0.18, H ±0.30, N ±0.30.
[c] In addition acetophenone azine, m.p. 124–125°C, was isolated in 26% yield.
[d] The substrate was prepared *in situ* from pyridine-4-carboxaldehyde and **2c**, and not isolated. The only product obtained in the reaction was believed to be 4-methoxymethylpyridine (57% yield).

2,4,6-Triisopropylbenzenesulphonyl Hydrazones 3c:

Procedure A: The carbonyl compound **1** (10 mmol) is added in one portion to a freshly prepared magnetically-stirred solution of 2,4,6-triisopropylbenzenesulphonyl hydrazide[5] (**2c**, 3.3 g, 11 mmol) in methanol (45 ml) at room temperature. After 1 h, the products are transferred to a refrigerator and kept at ~4°C overnight. The crystalline precipitate is collected by filtration and, if necessary, further crops are obtained by concentrating the mother liquors or by diluting them with water.

Procedure B: This is the same as procedure A except that concentrated hydrochloric acid (0.25 ml) is added to the reaction medium.

Aryldiazoalkanes 4:

The 2,4,6-triisopropylbenzenesulphonyl hydrazone **3c** (5 mmol), potassium hydroxide (0.56 g, 10 mmol), and methanol (15 ml) are heated, under reflux, until (see Table 2) no **3c** remains [as indicated by T.L.C. on Merck silica gel 60 F_{254} plates, developed in chloroform/methanol (9:1 v/v)]. The products are then cooled, diluted with ice/water (100 g), and the resulting mixture is extracted with dichloromethane (4 × 20 ml). The combined extracts are washed with saturated aqueous sodium hydrogen carbonate (3 × 50 ml), dried with magnesium sulphate, and evaporated under reduced pressure to give the aryldiazoalkane **4**.

Conversion of Aryldiazoalkanes 4 into the Corresponding 3,5-Dinitrobenzoate Esters 5:

For each of the entries 1–6 (Table 2), a solution of 3,5-dinitrobenzoic acid (2.12 g, 10 mmol) in dry tetrahydrofuran (25 ml) is added to the aryldiazoalkane **4** as obtained above. When nitrogen evolution ceases, the products are concentrated under reduced pressure and redissolved in dichloromethane (25 ml). The resulting solution is washed with saturated aqueous sodium hydrogen carbonate (3 × 50 ml), dried with

magnesium sulphate, and evaporated under reduced pressure. The yields indicated in Table 2 are based on the weights of crude (i.e. unrecrystallised) 3,5-dinitrobenzoate esters **5** obtained.

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