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USE OF 2,4,6-TRI-ISOPROPYLBENZENESULPHONYL HYDRAZIDE IN THE McFADYEN-STEVENS ALDEHYDE SYNTHESIS

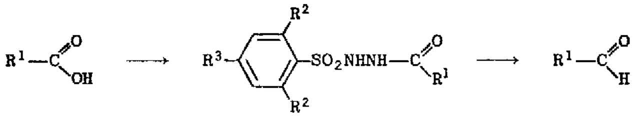
Christopher C. Dudman, Peter Grice and Colin B. Reese*

Department of Chemistry, King's College, Strand, London WC2R 2LS, England

Summary: Aroyl derivatives of 2,4,6-tri-isopropylbenzenesulphonyl hydrazide decompose readily in the presence of potassium carbonate in boiling methanol solution to give aldehydes and varying quantities of the corresponding alcohols and methyl esters. The formation of the latter by-products is suppressed and good yields of aldehydes are obtained when hydrazine is added to the reaction medium.

The McFadyen-Stevens procedure[1,2] for reducing carboxylic acids (*1*), *via* the corresponding 1-acyl-2-(toluene-*p*-sulphonyl)hydrazines (*2c*), to aldehydes (*3*) is outlined in Scheme 1. In the original procedure[1], aromatic aldehydes (*3*; R^1 = aryl) were prepared by heating the acyl derivatives (*2c*) with an excess of sodium carbonate in ethylene glycol at 160°C for 75 sec. Newman and Caflisch[3] later confirmed that the reaction conditions were critical and showed that the reaction was catalyzed by finely divided solids (e.g. powdered soft glass). Sprecher *et al.* showed[4] that aliphatic aldehydes containing no $\underline{\alpha}$-protons (e.g. *3*; R^1 = Me$_3$C) could be prepared by the McFadyen-Stevens procedure and Babad *et al.* then showed[5] that simple aliphatic aldehydes [e.g. *3*; R^1 = CH$_3$(CH$_2$)$_2$ and (CH$_3$)$_2$CH] could also be prepared by flash pyrolysis of 1-acyl-2-(toluene-*p*-sulphonyl)hydrazines (*2c*) in the presence of base. Recently, Nair and Shechter[6] have obtained good yields of both aromatic and aliphatic aldehydes by the vacuum pyrolysis of alkali metal salts of 1-acyl-2-(toluene-*p*-sulphonyl)hydrazines (*2c*).

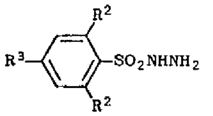
<u>Scheme 1</u>



1

2 *a*; R^2 = R^3 = Me$_2$CH
b; R^2 = R^3 = Me
c; R^2 = H, R^3 = Me

3



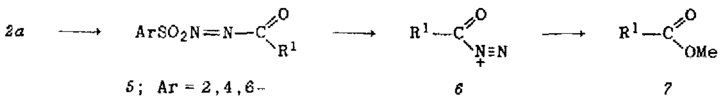
4 *a*; R^2 = R^3 = Me$_2$CH
b; R^2 = R^3 = Me
c; R^2 = H, R^3 = Me

Several years' ago, we observed[7] that 2,4,6-tri-isopropylbenzene- and mesitylene-2-sulphonyl hydrazides (*4a* and *4b*, respectively) underwent base-catalyzed decomposition in deuteriomethanol solution at *ca.* 380 and 16 times, respectively, the rate of toluene-*p*-sulphonyl hydrazide (*4c*). We attributed[7] these rate enhancements to the greater release of steric compression in the decomposition of arenesulphonyl hydrazides with bulky *ortho*-substituents and later exploited this phenomenon in a nitrile synthesis[8]. We now report on the use of 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (TPSH, *4a*) in the McFadyen-Stevens aldehyde synthesis.

The required 1-acyl-2-arenesulphonylhydrazine derivatives (*2a*) were prepared by allowing acyl chlorides to react with TPSH[7,8] (*4a*; 1.1 molecular equivalents) in anhydrous pyridine solution at 0°C; these intermediates were isolated as crystalline solids in satisfactory yields (Table) and were characterized on the basis of microanalytical and spectroscopic data. When 1-acyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazines (*2a*; 5 mmol), derived from aromatic carboxylic acids, were heated under reflux with anhydrous potassium carbonate (10 mmol) in methanol (15 ml), they underwent complete decomposition (as indicated by t.l.c.) within 15-60 min [see Table, experiments nos. 1-3 and 6-12]. The decomposition, under the same conditions, of the only two aliphatic acyl derivatives (*2a*; $R^1 = Me_3C$ and cyclohexyl) examined occurred more slowly but was complete within 2.5 hr [experiments nos. 13 and 14]. The relative rates of decomposition of the 3-toluoyl derivatives (*2a*, *2b* and *2c*; $R^1 = 3\text{-}MeC_6H_4$) of TPSH (*4a*), mesitylene-2-sulphonyl hydrazide (*4b*) and toluene-*p*-sulphonyl hydrazide (*4c*), respectively were found [experiments nos. 3-5] to be *ca*. 180:30:1. It was therefore clear that, as anticipated[7,8], bulky *ortho*-substituents had a profound effect on the rates of decomposition of 1-acyl-2-arenesulphonylhydrazines (*2*).

Although the decomposition of 1-acyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazines (*2a*) occurred under relatively mild conditions, the yields of aldehydes obtained were unsatisfactory. For example, the benzoyl derivative (*2a*; $R^1 = Ph$) underwent complete decomposition within 30 min [Table, experiment no. 1] but the yield of benzaldehyde (isolated as its crystalline 2,4-dinitrophenylhydrazone) was only 36%. Small quantities (7 and 8%, respectively) of methyl benzoate and benzyl alcohol were also obtained. It can be seen from the Table that similar results were obtained with most of the other aroyl derivatives (*2a*) of TPSH examined [experiments nos. 2-3 and 6-12]. In the cases of the aliphatic acyl derivatives (*2a*; $R^1 = Me_3C$ and cyclohexyl), substantial yields of the corresponding methyl esters but no detectable quantities of aldehydes were obtained [experiments nos. 13-14].

Scheme 2



The unsatisfactory yields of aromatic aldehydes obtained following the decomposition of the acyl derivatives (*2a*) of TPSH were found not to be due to the aldehydes undergoing Cannizzaro reactions. Thus when benzaldehyde and *p*-anisaldehyde [see experiments nos. 1 and 11] were each heated with a twofold excess of potassium carbonate in boiling methanol solution for 25 min, the corresponding methyl esters and alcohols could not be detected in the products. Indeed both aldehydes were recovered from the reaction mixtures in *ca*. 90% yields. Trimethylacetaldehyde [see experiment no. 13] was found to be similarly stable to potassium carbonate in boiling methanol solution. Despite the non-occurrence of Cannizzaro reactions under the experimental conditions, it seems likely[9] that the alcohol products result from the reduction of the corresponding aldehydes. However, the detailed mechanism involved in this process has not yet been elucidated. While the formation of methyl esters may accompany this reduction

TABLE. Reactions Between 1-Acyl-2-arenesulphonylhydrazines (*2*) and Potassium Carbonate in Boiling Methanol Solution.

Expt. No.	Substrate	Yield (%)	M.p. (°C)	Reaction Time (min)	Estimated Yield of R^1CHO (%)[a]	Estimated Yield of R^1CO_2Me (%)[b]	Estimated Yield of R^1CH_2OH (%)[b]
1	*2a*; R^1 = Ph	75	210 - 212 (dec)	30	36 (84)	7	8
2	*2a*; R^1 = 2-MeC_6H_4	70	159 - 160	60	54 (74)	9	12
3	*2a*; R^1 = 3-MeC_6H_4	79	205 - 206	40	49 (80)	11	9
4	*2b*; R^1 = 3-MeC_6H_4	86	159 - 159.5	240	66	4	8
5	*2c*; R^1 = 3-MeC_6H_4	83	138 - 139	7080	46	-	14
6	*2a*; R^1 = 4-MeC_6H_4	83	195 - 196	15	57 (90)	18	12
7	*2a*; R^1 = 2-ClC_6H_4	60	159 - 161	25	41 (67)	3	7
8	*2a*; R^1 = 3-ClC_6H_4	65	196 - 197	25	52 (77)	4	4
9	*2a*; R^1 = 4-ClC_6H_4	76	189 - 190	25	46 (69)	4	5
10	*2a*; R^1 = 3-$O_2NC_6H_4$	75	187 - 188	55	32 (58)	1	3
11	*2a*; R^1 = 4-$MeOC_6H_4$	76	193 - 194	20	20 (77)	15	7
12	*2a*; R^1 = 3,4-$(MeO)_2C_6H_3$	79	216 - 217	15	45 (63)	25	12
13	*2a*; R^1 = Me_3C	73	135 - 136	150	-	∿60	
14	*2a*; R^1 = cyclohexyl	66	188 - 189	150	-	∿60	

[a] Based on isolated crystalline 2,4-dinitrophenylhydrazones. The numbers in parentheses represent the percentage isolated yields of 2,4-dinitrophenylhydrazones when hydrazine hydrate (4.0 molecular equivalents with respect to substrate) was added to the reaction mixture.

[b] These estimates were made by comparing the integrals of the resonance signals of methyl ($-CO_2Me$) or methylene ($-CH_2OH$) protons with those of the aldehyde ($-CHO$) protons in the n.m.r. spectra of the crude products.

reaction, an alternative route for their formation is indicated in Scheme 2. It is suggested that atmospheric oxidation of the 1-acyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazines (*2a*) to the corresponding azo-compounds (*5*) can compete with their base-catalyzed fragmentation (Scheme 1) to give aldehydes (*3*). If such oxidation occurs, then the formation of methyl esters (*7*) by the solvolysis of the intermediate acyl diazonium ions (*6*) would not be unexpected. If this hypothesis is correct, then it would appear that acyl derivatives (*2a*) of the very bulky TPSH (*4a*) are particularly susceptible to oxidation. Thus no methyl ester was detected in the decomposition products of 1-(3-toluoyl)-2-(toluene-*p*-sulphonyl)hydrazine (*2c*; $R^1 = 3\text{-}MeC_6H_4$) [Table, experiment no. 5].

It was found that the formation of aromatic methyl esters and alcohols could virtually be suppressed by the addition of hydrazine hydrate and a trace of copper(II) sulphate to the reaction mixtures. For example, when 1-benzoyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazine (*2a*; $R^1 = Ph$, 5 mmol), potassium carbonate (10 mmol), hydrazine hydrate (20 mmol) and 0.1 *M* - aqueous copper(II) sulphate (1 drop) were heated, under reflux, in methanol (15 ml) for 30 min, no methyl benzoate or benzyl alcohol could be detected in the products. When the latter products which, after removal of the 2,4,6-tri-isopropylbenzenesulphinate, appeared to consist of hydrazine derivatives of benzaldehyde[10], were treated with 2,4-dinitrophenylhydrazine and sulphuric acid in aqueous methanol, benzaldehyde 2,4-dinitrophenylhydrazone was obtained and isolated as a crystalline solid, m.p. 234°C (lit.[11] 237°C), in 84% yield [Table, experiment no. 1]. Even in those cases in which the decomposition of aroyl derivatives (*2a*; R^1 = aryl) of TPSH led to the largest quantities of methyl esters and alcohols [experiments nos. 6, 11, 12], the addition of an excess of hydrazine hydrate virtually suppressed their formation and led to satisfactory yields of aldehydes (as hydrazine derivatives) which were then isolated as their 2,4-dinitrophenylhydrazones [Table]. Only in the case of the aliphatic acyl derivatives (*2a*; $R^1 = Me_3C$ and cyclohexyl) [experiments nos. 13 and 14] did the addition of hydrazine hydrate appear to have no significant effect. The precise mode of action of hydrazine in suppressing the formation of aromatic alcohols and methyl esters in the potassium carbonate-promoted decomposition of 1-aroyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazines (*2a*; R^1 = aroyl) is not clear. While its main effect may be to derivatize and hence to protect the aldehydes against reduction as soon as they are formed, it may also act as a source of di-imide[12] which can reduce any azo-compounds (*5*) formed back to the corresponding hydrazine derivatives (*2a*).

In conclusion, although the use of TPSH (*4a*) instead of toluene-*p*-sulphonyl hydrazide (*4c*) in the McFadyen-Stevens reaction leads to much milder reaction conditions, we have so far only succeeded in obtaining good yields of aldehydes (and then only aromatic aldehydes) when hydrazine hydrate was added to the reaction medium. The aldehydes were then isolated as hydrazine derivatives[10] but were converted into the corresponding 2,4-dinitrophenylhydrazones usually in good yields. As aldehydes may readily be regenerated from the latter derivatives and apparently also from simple hydrazine derivatives[13], the work reported here represents a useful modification of the McFadyen-Stevens reaction which could find application in the preparation of aromatic aldehydes when particularly mild reaction conditions are desirable.

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[9] When 1-(*p*-anisoyl)-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazine (*2a*; $R^1 = 4\text{-MeOC}_6H_4$) [5 mmol], benzaldehyde [5 mmol] and potassium carbonate [10 mmol] were heated together, under reflux, in methanol (15 ml) for 25 min, *ca.* one-half of the benzaldehyde was reduced to benzyl alcohol and the quantities of *p*-anisaldehyde and methyl *p*-anisate in the products were approximately equal. No methyl benzoate and virtually no *p*-methoxybenzyl alcohol could be detected in the products.

[10] The ^{1}H n.m.r. spectra of the products obtained in this and in related experiments (nos. 2-3 and 6-12) displayed no signals assignable to the resonances of aldehyde protons but they contained singlets in the region $\delta 7.5$-9 which were assigned to the resonances of the methine protons of hydrazones and azines.

[11] Z. Rappoport, "Handbook of Tables for Organic Compound Identification", 3rd Edn., CRC, Cleveland, 1967, p.147.

[12] In the presence of Cu^{2+} ions, hydrazine is reported [E.J. Corey, W.L. Mock and D.J. Pasto, *Tetrahedron Letters* 347 (1961)] to undergo oxidation to give di-imide. The latter could then reduce azo-compounds (*5*), if formed, back to the original hydrazine derivatives (*2a*).

[13] Preliminary experiments have suggested that treatment of the aldehyde derivatives [obtained when the decomposition of 1-acyl-2-(2,4,6-tri-isopropylbenzenesulphonyl)hydrazines (*2a*) is carried out in the presence of hydrazine] with sodium nitrite in acetic acid [L. Caglioti, F. Gasparrini, D. Misiti and G. Palmieri, *Synthesis* 207 (1979)] leads to the regeneration of the free aldehydes.

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