

## Diazo Transfer Reactions under Mildly Basic Conditions

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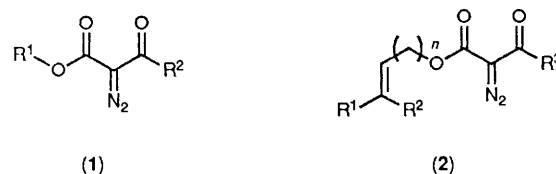
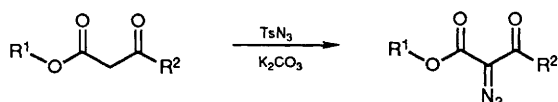
Practically quantitative diazo transfer from toluene-*p*-sulphonyl azide to active methylene compounds has been achieved rapidly under mildly basic conditions with potassium carbonate in acetonitrile.

Organic  $\alpha$ -diazo carbonyl compounds have found widespread use in the synthesis of complex organic molecules. In connection with work aimed at developing chiral catalysts for carbenoid addition reactions, we needed a general synthetically reliable method for producing various  $\alpha$ -diazo carbonyl derivatives. Base catalysed diazo transfer reactions from an arenesulphonyl azide to active methylene compounds are well documented.<sup>1</sup> Variations of the reagents<sup>2–4</sup> and methods aiding separation of unreacted diazo transfer agent from the product mixture<sup>5</sup> have been described. Prolonged reaction times, elevated reaction temperatures, and use of highly specialized reagents still limit the existing methodology. We have developed a simple, rapid, and high-yielding method for diazo transfer reactions that overcomes the known limitations of prior methods.

The base generally used for diazo transfer reactions from toluene-*p*-sulphonyl azide<sup>6</sup> is triethylamine ( $pK_a$  11), obviously not basic enough to ensure complete reaction of malonates and  $\beta$ -keto esters.<sup>7</sup> Phase transfer catalysis has also been described,<sup>8</sup> but this method is not suitable for compounds sensitive to aqueous base catalysed hydrolysis (*e.g.*, methyl esters). Bearing these limitations in mind, we decided to look for other methods employing toluene-*p*-sulphonyl azide<sup>6</sup> as the transfer reagent to solve the problem.

Consideration of the solubilities of inorganic bases in organic solvents eventually led us to select potassium carbonate/acetonitrile as the base/solvent system.<sup>9</sup> Under these conditions, the reactions were usually complete in less than 1 h. The work-up simply consists of filtration of the inorganic salts and the sulphonamide by-product after addition of a non-polar organic cosolvent. The product is recovered in a state suitable for further operations, but can be distilled without appreciable loss in yield. No problems associated with hydrolysis of base-sensitive methyl acetoacetate were encountered,<sup>8b</sup> as can be seen from the results in Table 1.<sup>†</sup>

We have observed that no excess base is required, and simply using an equimolar amount of potassium carbonate is sufficient. For operational convenience, all diazo transfer reactions were carried out at room temperature. The reaction time depends on at least two further variables: the structure of the 1,3-dicarbonyl compound and the concentration. Thus, the reaction is more rapid for acetoacetates (about 15–20



<sup>†</sup> All new compounds were characterized by their satisfactory elemental analyses, and IR and NMR spectral data.

**Table 1.** Yields of diazo transfer using toluene-*p*-sulphonyl azide and calcined K<sub>2</sub>CO<sub>3</sub> in acetonitrile.

Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<i>n</i>	Yield <sup>a</sup> /%
(1a)	Me	Me	—	—	96
(1b)	Bu <sup>t</sup>	OEt	—	—	86
(2a)	H	H	OBu <sup>t</sup>	1	95
(2b)	H	H	OMe	1	99
(2c)	H	H	NEt <sub>2</sub>	1	96
(2d)	H	H	OBu <sup>t</sup>	2	92
(2e)	H	H	OMe	2	96
(2f)	Me	Me	OBu <sup>t</sup>	1	86
(2g)	Me	Me	OMe	1	74

<sup>a</sup> Yields refer to distilled materials.

min) than for methyl malonates (about 1 h) or *t*-butyl malonates (4–5 h).<sup>‡</sup> We have achieved good results when the concentrations were adjusted such that a final concentration of *ca.* 0.5 M for the diazo compound is reached. These conditions are preferred to a two-phase system because either hydroxide or carbonate can cause hydrolysis of esters derived from primary alcohols.

A typical experimental procedure for the preparation of methyl 2-diazo-3-oxobutyrate follows. Methyl 3-oxobutyrate (580 mg, 5 mmol, 100 mol%) was dissolved in anhydrous acetonitrile (5 ml), and solid calcined potassium carbonate (690 mg, 5 mmol, 100 mol%) was added. The flask was fitted with a balloon of nitrogen, and a solution of toluene-*p*-sulphonyl azide (955 mg, 5 mmol, 100 mol%) in anhydrous

<sup>‡</sup> For *t*-butyl ethyl malonate, the PTC (phase transfer catalysis) method<sup>8</sup> either failed completely (Na<sub>2</sub>CO<sub>3</sub>) or gave only ester hydrolysis products (NaOH). Triethylamine catalysed diazo transfer<sup>6</sup> was very slow (*ca.* 70% complete after 24 h).

acetonitrile (4 ml) was added. The mixture was stirred until the reaction was complete as judged by TLC. Ether (10 ml) was added to precipitate the salts, and the mixture was filtered through celite. The filter cake was washed with ether, and the organic solvents were removed *in vacuo*. Hexane : ether (2 : 1) was added to the residual oil to precipitate the tosyl amide. The solid was filtered, and concentration of the filtrate gave the crude product as an oil. Purification was effected by Kugelrohr distillation to give methyl 2-diazo-3-oxobutyrate (680 mg, 4.8 mmol, 96%) as a yellow oil.

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