Diazo Transfer Reactions to 1,3-Dicarbonyl Compounds with Tosyl azide
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Abstract: A practical protocol for the large scale preparation of 2-diazo-1,3-dicarbonyl compounds is described by diazo transfer reactions with tosylazide followed by efficient chromatographic purifications on silica gel and/or alumina.

Key words: diazo compounds; ketones; esters; Regitz reaction; chromatography.

Diazotization reactions of 1,3-dicarbonyl compounds is commonly used in organic synthesis and new methods for their preparation are constantly developed. In the case of compounds bearing an active methylene, the Regitz reaction using p-toluenesulfonyl azide (TsN₃) as the diazo transfer reagent remains the most efficient approach despite it is hampered by potential hazard and purification problems to remove the p-tosylamide co-product. Several alternative diazo transfer reagents have been proposed to circumvent these problems (Figure 1). For example, methanesulfonyl azide (MsN₃) and p-acetamidobenzensulfonyl azide (p-ABSA) have been found efficient complementary reagents but with similar purification issues. A polystyrene-supported benzensulfonyl azide (PS-SO₂N₃) has been proposed as a safer alternative to TsN₃, which also solved the purification problem by elimination of the polystyrene-supported benzensulfonylamine co-product by simple filtration, but the cost of the reagent is prohibitive when compared to other diazo transfer reagents. More recently, imidazole-1-sulfonyl azide hydrochloride (Im-SO₂N₃) has advantageously been introduced as an efficient reagent for diazo transfer reactions to primary amines (when compared to the standard trifluoromethanesulfonyl azide, T[N₃]Cl), but its efficiency in diazo transfer reactions to activated methylene compounds is moderate. Even more recently, 2-azido-1,3-dimethylimidazolinium chloride (ADMC) revealed as an effective diazo transfer reagent to activated methylene compounds. This new reagent is not sulfonyl azide-based, thus avoiding the purification problems associated with the formation of the corresponding sulfonylamide co-product, but due to its hygroscopic character the reagent must be prepared in situ immediately before use. The corresponding 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP) was also prepared, and found less hygroscopic and easier to handle.

Entry | Substrate | Conditions | Products | Yield
--- | --- | --- | --- | ---
1 | 2a | 22% | 2b | 90% (40 grams scale)
efficient, while 2-ABSA<sup>14</sup> and ADMP<sup>13b</sup> were reported to give lower yields of 2a and 2b, respectively. Similar conditions were applied to the representative 1,3-diketones 1c and 1d, and the 1,3-ketoester 1e, which allowed the isolation of the corresponding 2-diazoo compounds 2c-e in good yields following SiO<sub>2</sub> and/or Al<sub>2</sub>O<sub>3</sub> chromatography without detectable contamination by <sub>p</sub>-tosylamide (by <sup>1</sup>H NMR).

In conclusion, despite efforts to discover an ideal diazo-transfer reagent, multigram-scale syntheses of 2-diazoo-1,3-dicarbonyl compounds are still very competitively performed with tosyl azide, and the problem of <sub>p</sub>-tosylamide contamination can be solved by short chromatographic purifications on silica gel and/or alumina.

**Caution!** Azide reagents are potentially hazardous.<sup>8</sup> Reactions were generally carried out under argon atmosphere. All reagents and solvents were used as received from commercial sources. Anhydrous solvents were obtained from an automated solvent purification system. TLC analysis was performed on Merck 60F254 plates and visualized under UV (254 nm) or with <sub>p</sub>-anisaldehyde and H<sub>2</sub>SO<sub>4</sub> in EtOH. Flash chromatographies were performed with Merck 40-63 µm silica gel, and/or Merck 63-200 µm aluminium oxide 90 basic, and/or Merck 63-200 mm aluminium oxide 90 neutral. PE refers to the fraction of petroleum ether that was distilled between 40 and 65 ºC. NMR data were recorded on a Bruker Avance 300 spectrometer in CDCl<sub>3</sub>. Chemical shifts are given in ppm using as internal standards the residual CHCl<sub>3</sub> signal for <sup>1</sup>H NMR (δ = 7.26) and the deuterated solvent signal for <sup>13</sup>C NMR (δ = 77.0).

### Tosyl azide (TsN<sub>3</sub>)

This procedure is a slight modification of Regitz’s procedure.<sup>13d</sup> In a 1 L Erlenmeyer flask equipped with an adequate magnetic stirring bar, sodium azide (38.9 g, 0.60 mol) was solubilized in water (100 mL) and then diluted with acetone (100 mL). In a 500 mL Erlenmeyer flask, 2-<sub>p</sub>-tosyl chloride (103.7 g, 0.54 mol) was solubilized in acetone (500 mL), and this solution was added to the former. The resulting mixture was stirred at room temperature for 2 h, concentrated under vacuum, and transferred to a separatory funnel containing water (300 mL). The biphasic solution was shaken vigorously, decanted, and the collected organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and placed under high vacuum to afford 96.0 g (89%) of TsN<sub>3</sub> as a colorless oil (which should be stored at ca. +4 ºC).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 146.1 (C), 135.2 (C), 130.1 (2 CH), 127.2 (2 CH), 21.4 (CH<sub>3</sub>).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.79 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 2.43 (s, 3H).

### 2-Diazocyclohexane-1,3-dione (2a)

A 500 mL round-bottomed flask equipped with an adequate stirring bar was charged with cyclohexane-1,3-dione (1a, 36.4 g, 0.32 mol) and CH<sub>2</sub>Cl<sub>2</sub> (150 mL). Tosyl azide (64.0 g, 0.32 mol) and potassium carbonate (49.3 g, 0.36 mol) were successively added to the reaction and the mixture was stirred for 13 h at room temperature. The reaction mixture was then filtered through a pad of silica gel (rinsed out with CH<sub>2</sub>Cl<sub>2</sub>) and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography (500 g of SiO<sub>2</sub> eluted with 2:8 EtOAc/PE, and then 250 g of basic Al<sub>2</sub>O<sub>3</sub> eluted with 2:8 EtOAc/PE) afforded 40.4 g (90%) of 2a as a yellowish solid (which should be stored at ca. −25 ºC).

Rf (3:7 EtOAc/PE) = 0.37

Mp = 48-49 ºC (amorphous) [lit.<sup>14</sup> 48-49 ºC (Et<sub>2</sub>O)]

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 190.2 (2 C), 84.7 (C), 36.6 (2 CH<sub>2</sub>), 18.4 (CH<sub>3</sub>)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 2.50 (t, J = 6.4 Hz, 4H), 2.03-1.95 (m, 2H)
2-Diazodimethane (2b)
A 500 mL round-bottomed flask equipped with an adequate stirring bar was charged with dimezone (1b, 36.4 g, 0.26 mol) and CH$_2$CN (150 mL). Tosyl azide (51.2 g, 0.26 mol) and potassium carbonate (39.5 g, 0.29 mol) were successively added to the reaction and the mixture was stirred for 13 h at room temperature. The reaction mixture was then filtered through a pad of silica gel (rinsed out with CH$_2$Cl$_2$) and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography (500 g of SiO$_2$ eluted with 2.8 EtOAc/PE, twice) afforded 40.4 g (94%) of 2b as a white-greenish solid (which should be stored at ca. +4 °C).

**References**

(1) For efforts to clarify the terminologies of MBFTs, see:


