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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.

Sequential multiple bond-forming transformations (MBFTs), which include consecutive and domino multicomponent reactions (MCRs),[1] allow the preparation of diverse and sometimes impressively complex molecules in a single chemical operation. Some families of densely functionalized small organic molecules are well suited for use in these reactions. In connection with our program on the use of 1,3-dicarbonyl compounds in MBFTs,[2] we have recently introduced acylketenes obtained by microwave-assisted Wolff rearrangement[3] of 2-diazo-1,3-diketones as particularly valuable substrates in domino MCRs.[4]

Diazo compounds are commonly used in organic synthesis[5] and new methods for their preparation are constantly developed.[6] In the case of compounds bearing an active methylene, the Regitz reaction[7] using *p*-toluenesulfonyl azide (TsN_3) as the diazo transfer reagent remains the most efficient approach despite it is hampered by potential hazard[8] 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 (MsN_3)[9] and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[10] have been found efficient complementary reagents but with similar purification issues. A polystyrene-supported benzenesulfonyl azide (PS-SO_2N_3)[11] has been proposed as a safer alternative to TsN_3, which also solved the purification problem by elimination of the polystyrene-supported benzenesulfonamide 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-SO_2N_3) has advantageously been introduced as an efficient reagent for diazo transfer reactions to primary amines (when compared to the standard trifluoromethanesulfonyl azide, TfN_3),[12] 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.[13a] 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.[13b]

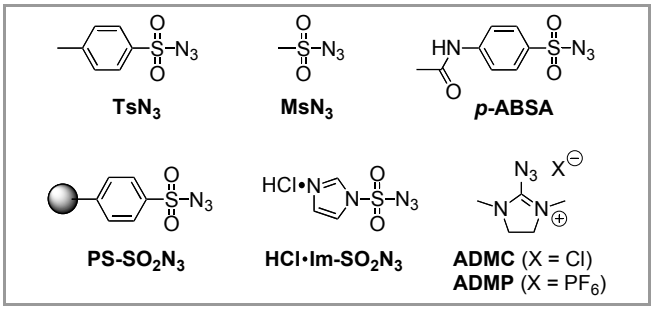
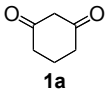
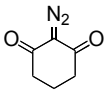
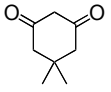
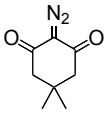
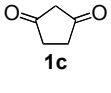
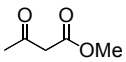
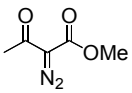


Figure 1 Representative diazo transfer reagents

In the past few years, we have repeatedly prepared in our laboratory several 2-diazo-1,3-dicarbonyl compounds from the corresponding 1,3-dicarbonyl compounds (Table 1). Representative diazo transfer reagents were tested, and it was found that TsN_3 combined with efficient chromatographic purification on silica gel and/or alumina gave the most satisfactory and reproducible results. The diazotation reactions of cyclohexan-1,3-diones **1a** and **1b** served as model reactions. In early trials with TsN_3 as the diazo transfer reagent under standard conditions (entry 1), the corresponding diazo compound **2a** was always contaminated by *p*-tosylamide (ca. 10-20%) following silica gel chromatography. After optimization of the purification procedure, it was found that iterative short chromatography on first silica gel (500 g) and then basic alumina (250 g) could solve this problem and allow the isolation of pure **2a** with 90% yield on a 40 grams scale. For comparison purpose, the results of diazo transfer reactions to **1a** or **1b** with *p*-ABSA, PS-SO_2N_3, Im-SO_2N_3 and ADMP are also given in Table 1 (entries 2-4 and 6, respectively). In our hands, the reaction with PS-SO_2N_3 afforded **2a** in excellent yield and without purification problem, but the cost of PS-SO_2Cl precluded its utilization on a 40-gram scale in our laboratory, and Im-SO_2N_3 was found less

Table 1 Diazo transfer reactions

Entry	Substrate	Conditions	Products	Yield

1	 **1a**	**TsN_3** (1 equiv), K_2CO_3 (1.1 equiv), MeCN, rt	 **2a**	90%
2	**1a**	***p*-ABSA** (0.81 equiv), KF (6 equiv), CH_2Cl_2, rt	**2a**	76%[a]
3	**1a**	**PS-SO_2N_3** (1 equiv), NEt_3 (1.1 equiv), MeCN, rt	**2a**	97%
4	**1a**	**Im-SO_2N_3** (1.2 equiv), K_2CO_3 (5 equiv), MeCN, rt	**2a**	36%
5	 **1b**	**TsN_3** (1 equiv), K_2CO_3 (1.1 equiv), MeCN, rt	 **2b**	94%
6	**1b**	**ADMP** (1.2 equiv), NEt_3 (2 equiv), 0 ºC, MeCN /THF (1:4)	**2b**	86%[b]
7	 **1c**	**TsN_3** (1 equiv), NEt_3 (1.1 equiv), MeCN, rt	 **2c**	86%[c]
8	 **1d**	**TsN_3** (1 equiv), K_2CO_3 (1.1 equiv), MeCN, rt	 **2d**	83%[d]
9	 **1e**	**TsN_3** (1 equiv), K_2CO_3 (1.1 equiv), MeCN, rt	 **2e**	90%[e]

[a] Ref 14.
[b] Ref 13b.
[c] Yield not reported in ref 15 and citing papers.
[d] 83% with ADMP in ref 13b, and 70% with TsN_3 in ref 16.
[e] 92% with *p*-ABSA in ref 17.

efficient, while *p*-ABSA[14] and ADMP[13b] 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-diazo compounds **2c-e** in good yields following SiO_2 and/or Al_2O_3 chromatography without detectable contamination by *p*-tosylamide (by ^1H NMR).

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

Caution! Azide reagents are potentially hazardous.[8]

Reactions were generally carried out under an 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 *p*-anisaldehyde and H_2SO_4 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 $CDCl_3$. Chemical shifts are given in ppm using as internal standards the residual $CHCl_3$ signal for ^1H NMR (δ = 7.26) and the deuterated solvent signal for ^{13}C NMR (δ = 77.0).

Tosyl azide (TsN_3)

This procedure is a slight modification of Regitz's procedure.[7d] 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, *p*-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_2SO_4, filtrated and placed under high vacuum to afford 96.0 g (89%) of TsN_3 as a colorless oil (which should be stored at ca. +4 ºC).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.1 (C), 135.2 (C), 130.1 (2 CH), 127.2 (2 CH), 21.4 (CH_3).

^1H NMR (300 MHz, $CDCl_3$): 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_3CN (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_2Cl_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, and then 250 g of basic Al_2O_3 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.[14] = 48-49 ºC (Et_2O)]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.2 (2 C), 84.7 (C), 36.6 (2 CH_2), 18.4 (CH_2)

^1H NMR (300 MHz, $CDCl_3$): δ = 2.50 (t, *J* = 6.4 Hz, 4H), 2.03-1.95 (m, 2H)

2-Diazodimedone (2b)

A 500 mL round-bottomed flask equipped with an adequate stirring bar was charged with dimedone (**1b**, 36.4 g, 0.26 mol) and CH_3CN (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_2Cl_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 ºC).

Rf (4:6 EtOAc/PE) = 0.58

Mp = 104-107 ºC (amorphous) [lit.[18] = 108 ºC (*i*PrOH)]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.5 (2 C), 83.3 (C), 50.2 (2 CH_2), 30.8 (C), 28.1 (2 CH_3)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 4H), 1.02 (s, 6H)

2-Diazocyclopentane-1,3-dione (2c)

A 100 mL round-bottomed flask protected from sunlight with an aluminum foil equipped with an adequate stirring bar was charged with cyclopentane-1,3-dione (**1c**, 1.47 g, 15 mmol) and CH_3CN (5 mL). Tosyl azide (2.96 g, 15 mmol) and triethylamine (2.30 mL, 16.5 mmol) were successively added to the reaction and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated under vacuum to give the crude product and purification of this material by flash chromatography (250 g of neutral Al_2O_3 eluted with 4:6 EtOAc/PE) afforded 1.59 g (86%) of **2c** as a yellowish solid (which should be protected from light and stored at ca. –25 ºC).

Rf (4:6 EtOAc/PE) = 0.25

Mp = 63-64 ºC (amorphous) [lit.[15] = 64-66 ºC]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.0 (2 C), 33.9 (2 CH) ($C=N_2$ not detected)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (s, 4H)

2-Diazoacetylacetone (2d)

A 250 mL round-bottomed flask equipped with an adequate stirring bar was charged with acetylacetone (**1d**, 10.0 mL, 97.4 mmol) and CH_3CN (90 mL). Tosyl azide (19.2 g, 97.4 mmol) and potassium carbonate (14.8 g, 107.1 mmol) were successively added to the reaction and the mixture was stirred for 1 h at room temperature. The reaction mixture was then filtered through a pad of celite (rinsed out with CH_2Cl_2) and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography (125 g of SiO_2 eluted with 3:7 EtOAc/PE, and then 250 g of basic Al_2O_3 eluted with 3:7 EtOAc/PE) afforded 10.2 g (83%) of **2d** as a yellow oil (which should be stored at ca. +4 ºC).

Rf (2:8 EtOAc/PE) = 0.24

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9 (2 C), 84.3 (C), 28.1 (2 CH_3)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 6H)

Methyl 2-diazoacetylacetate (2e)

A 250 mL round-bottomed flask equipped with an adequate stirring bar was charged with methyl acetoacetate (**1e**, 10.0 mL, 92.7 mmol) and CH_3CN (90 mL). Tosyl azide (18.3 g, 92.8 mmol) and potassium carbonate (14.1 g, 102.0 mmol) were successively added to the reaction and the mixture was stirred for 1 h at room temperature. The reaction mixture was then filtered through a pad of celite (rinsed out with CH_2Cl_2) and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography (125 g of SiO_2 eluted with 1:9 EtOAc/PE, and then 250 g of basic Al_2O_3 eluted with 2:8 EtOAc/PE) afforded 11.9 g (90%) of **2e** as a yellow oil (which should be stored at ca. +4 ºC).

Rf (2:8 EtOAc/PE) = 0.52

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.6 (C), 161.5 (C), 75.8 (C), 51.9 (CH_3), 27.8 (CH_3)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 2.36 (s, 3H)

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