The selective preparation and Suzuki coupling reactivity of cyclic 1,3-dione derived mono- and ditriflates

Michael C. Willis* and Christelle K. Claverie

Department of Chemistry, University of Bath, Bath BA2 7AY, UK

Received 18 May 2001; accepted 31 May 2001

Abstract—The combination of triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine was found to be a selective reagent system for the conversion of cyclic 1,3-diones to the corresponding monotriflate derivatives. The use of *N*-(5-chloro-2-pyridyl)triflimide together with KHMDS was selective for the preparation of the corresponding ditriflates. The Suzuki coupling reactivity of both the mono- and ditriflates was also explored. © 2001 Elsevier Science Ltd. All rights reserved.

Vinyl and enol triflates are proving to be extremely versatile coupling partners and have been shown to participate in a variety of cross-coupling reactions including variants of the Stille,[1] Suzuki[2] and Heck[3] reactions.[4] We proposed that the mono- and ditriflates, such as **2** and **3**, derived from cyclic 1,3-diones would be useful building blocks for use in target syntheses or as substrates for desymmetrisation studies.[5] We therefore set out to determine reaction conditions to allow the selective production of either the mono- or ditriflates. A concern at the outset of this study was the stability of the required triflates, and in particular their stability towards flash chromatography.

Initial attempts at the preparation of ditriflate **3** focused on the use of triflic anhydride in combination with a variety of bases, however, only low yields of ditriflate **3** were obtained with the monotriflate forming preferentially. Optimisation of these conditions (2 equiv. Tf₂O, 2.2 equiv. 2,6-di-*t*-Bu-4-Me-pyridine, DCE, 80°C)

allowed the monotriflate **2** to be obtained in good yield (Scheme 1).[6] The use of *N*-phenyl triflimide as the triflate source was similarly unsuccessful for the production of **3**.[7] However, the combination of the more reactive triflating reagent *N*-(5-chloro-pyridyl)triflimide **4** and KHMDS delivered the ditriflate **3** as the major product.[8] Optimised conditions involved treatment of diketone **1** with 2 equiv. of KHMDS followed by 2.2 equiv. of **4** in THF at −78°C to furnish the required ditriflate in 81% yield. Ditriflate **3** was isolated as an amorphous white solid that could be readily purified by crystallisation or flash chromatography upon silica gel.

These two sets of complimentary reaction conditions were then successfully applied to two further diketone substrates.[9] Both the mono- and ditriflate derived from the corresponding dimethylated 1,3-diketone were obtained in excellent yields (**5** 90% and **6** 92%, respectively, Fig. 1) and again both were stable to purification
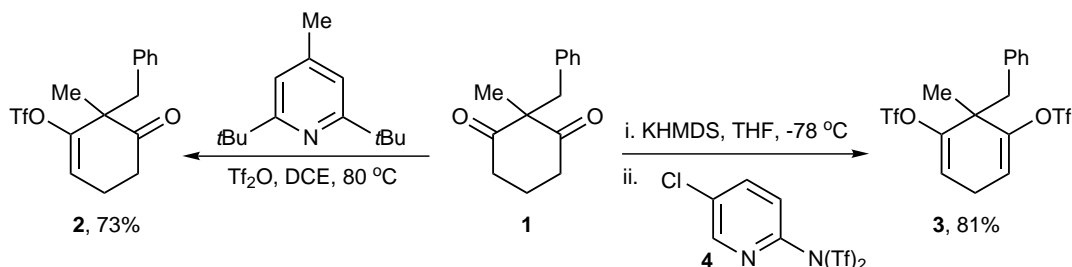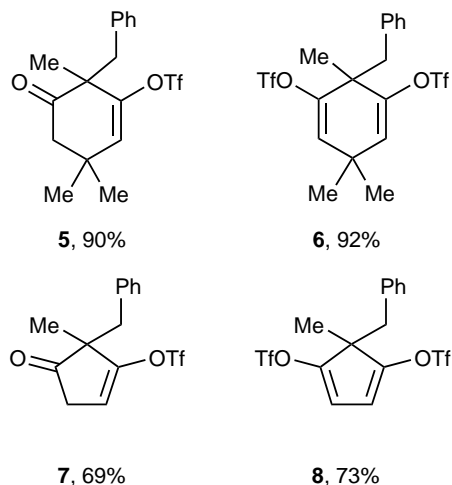

Scheme 1.

Figure 1.

by flash chromatography.[10] The two triflates originating from the cyclopenta-1,3-dione substrate were also obtained in good yields (69% monotriflate, 73% ditriflate).[11] Pleasingly, the potentially reactive conjugated diene system present in ditriflate **8** proved to be similarly stable to chromatography.

With the synthesis of the required mono- and ditriflates achieved, we chose to explore their reactivity in Suzuki cross-coupling reactions and these preliminary findings are presented below in Tables 1 and 2.[12] Gratifyingly, the six-membered monotriflate **2** underwent reaction with 4-methoxyphenylboronic acid **9** in the presence of Pd(OAc)$_2$ (10 mol%), PPh$_3$ and KOH, to deliver the coupled product in 91% yield (Table 1). Given the high steric-crowding in the immediate environment of the triflate functionality, the mild reaction conditions (room temperature) and short reaction time (40 min) for this transformation are particularly noteworthy.[13] The dimethylated analogue **5** also performs well delivering the coupled product in 69% yield after 80 min. Surprisingly, the five-membered monotriflate **7** showed poor reactivity and after 18 h reaction, only 12% of the coupled product was isolated.[14]

Table 1.
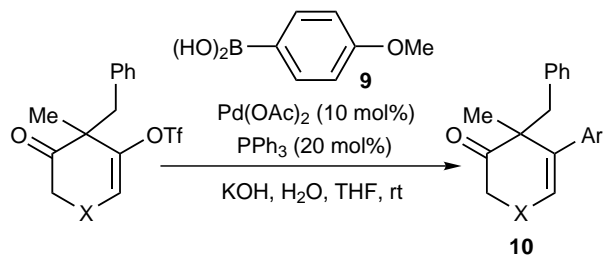
Substrate	X	Time	Yield **10** (%)
2	CH$_2$	40 min	91
5	C(Me)$_2$	80 min	69
7	–	18 h	12

Table 2.
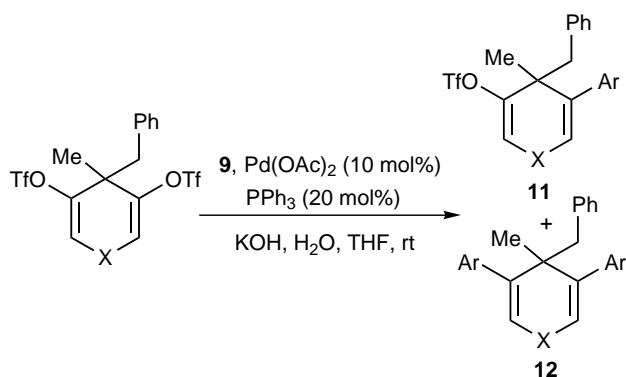
Substrate	X	Time (h)	Yield **11** (%)	Yield **12** (%)
3	CH$_2$	24.0	7	8
6	C(Me)$_2$	4.0	31	17
8	–	1.0	71	0

Of the ditriflate substrates the five-membered system **8** underwent facile coupling to provide the mono-coupled material in excellent yield; none of the dicoupled material was observed. The dimethylated six-membered system **6** also performed well showing good reactivity, although the desired mono-coupled material decomposed under the reaction conditions resulting in a low isolated yield. The unsubstituted six-membered substrate **3** performed poorly, yielding only low yields of the two coupling products.

The reason for the poor reactivity of both the five-membered monotriflate **7** and the six-membered ditriflate **3** is unclear at present. However, the allylic protons in both **3** and **7** are more acidic than those present in the other substrates, this combined with the use of KOH as base may be responsible for the observed poor reactivity.

In summary, we have described complementary conditions for the selective production of either the mono- or ditriflate derivatives from a range of cyclic 1,3-diones. We have also demonstrated that several of these highly functionalised substrates undergo facile Suzuki coupling reactions under mild conditions. Further studies on the coupling reactions of these substrates together with details of their use in desymmetrisation reactions will be reported in due course.

Acknowledgements

References

1. For some recent examples, see: (a) Dominguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5817–5925; (b) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131–8140.

2. For some recent examples, see: (a) Occhiato, E. G.; Trabacchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459–2465; (b) Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, *41*, 9083–9087.

3. For some recent examples, see: (a) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161–164; (b) Hynes, Jr., J.; Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647–4650.

4. For a review on the uses and preparations of triflate derivatives, see: Ritter, K. *Synthesis* **1993**, 735–762.

5. For a review on enantioselective desymmetrisation, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

6. All new compounds reported in this paper were fully characterised.

7. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.

8. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

9. Typical procedures for the preparation of the mono- and ditriflates are given below. Monotriflate **2**: A solution of trifluoromethanesulfonic anhydride (2.5 ml, 14.7 mmol) in dry DCE (5 ml) was added dropwise under nitrogen to a stirred mixture of the diketone **1** (1.51 g, 7 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (3.24 g, 15 mmol) in dry DCE (30 ml) at 0°C. The reaction was heated to 80°C for 18 h after which time the mixture was cooled to room temperature. Ether (150 ml) was added and the white pyridinium triflate salt was filtered, washed with ether (30 ml) and the filtrate was concentrated under reduced pressure to give a dark orange oil. The residue was purified by flash chromatography (gradient elution, 2–10% EtOAc/petrol) to give the monovinyltriflate as a yellow oil (1.78 g, 73%). Ditriflate **3**: A solution of potassium hexamethyldisilazide (0.5 M in toluene, 9.7 mmol) was added dropwise over 1 h to a stirred mixture of diketone **1** (1.00 g, 4.6 mmol) and *N*-(5-chloro-2-pyridyl)triflimide (5.90 g, 10.1 mmol) in dry THF (40 ml) at −78°C. The reaction mixture was stirred at this temperature for 1 h then it was slowly warmed to room temperature over 3 h. The mixture was diluted with hexane (90 ml), washed with water (50 ml), 10% NaOH (50 ml) and brine (50 ml). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a dark oil which was further purified by flash chromatography (gradient elution, 5–10% ether/petrol) to give the ditriflate **3** as a white solid (1.79 g, 81%).

10. For the preparation of a dinonaflate compound similar to ditriflate **5**, see: Bräse, S. *Synlett* **1999**, 1654–1656.

11. Representative data for compounds **2**, **3** and **5→8**. Monotriflate **2**: δ_H (400 MHz, $CDCl_3$) 7.28–7.20 (3H, m), 7.08–7.02 (2H, m), 5.97 (1H, dd, app. t, *J* 4.7 Hz), 3.17 (1H, d, *J* 13.7 Hz), 2.83 (1H, d, *J* 13.7 Hz), 2.40–2.32 (1H, m), 2.21–2.12 (1H, m), 1.95 (1H, dt, *J* 15.2, 5.9 Hz), 1.74–1.65 (1H, m), 1.42 (3H, s); δ_C (67.5 MHz, $CDCl_3$) 209.7, 149.9, 136.5, 130.3, 128.7, 127.4, 118.8, 118.1, 54.8, 43.1, 37.1, 23.4, 19.6. Found C, 51.5; H, 4.35; $C_{15}H_{15}O_4SF_3$ requires C, 51.7; H, 4.31%. Ditriflate **3**; δ_H (400 MHz, $CDCl_3$) 7.29–7.21 (3H, m), 7.10–7.06 (2H, m), 5.69 (2H, dd app. t, *J* 3.5, 4.1 Hz), 2.87 (2H, s), 2.76 (1H, dt, *J* 4.1, 22.8 Hz), 2.33 (1H, dt, *J* 3.5, 22.8 Hz), 1.55 (3H, s); δ_C (67.5 MHz, $CDCl_3$) 147.7, 135.0, 130.1, 128.5, 127.4, 118.7, 114.2, 45.0, 42.1, 24.5, 23.1. Found C, 40.0; H, 3.00, $C_{16}H_{14}O_6S_2F_6$ requires C, 40.0; H, 2.92%. Monotriflate **5**: δ_H (400 MHz, $CDCl_3$) 7.27–7.20 (3H, m), 7.09–7.05 (2H, m), 5.81 (1H, s), 3.09 (1H, d, *J* 13.4 Hz), 2.87 (1H, d, *J* 13.4 Hz), 2.26 (1H, d, *J* 14.7 Hz), 1.69 (1H, d, *J* 14.7), 1.41 (3H, s), 1.02 (3H, s), 0.47 (3H, s); δ_C (100 MHz, $CDCl_3$) 208.2, 147.8, 135.9, 130.1, 128.1, 127.4, 126.9, 118.3, 53.7, 51.4, 41.8, 32.5, 29.5, 28.5, 23.6; *m/z* (EI). Found M+NH_4^+, 394.1306, $C_{17}H_{23}SF_3NO_4$ requires 394.1300. Ditriflate **6**: δ_H (400 MHz, $CDCl_3$) 7.29–7.18 (3H), 7.06–7.03 (2H, m), 5.48 (2H, s), 2.85 (2H, s), 1.52 (3H, s), 1.09 (3H, s), 0.34 (3H, s); δ_C (100 MHz, $CDCl_3$) 145.6, 135.7, 130.1, 128.3, 127.3, 124.3, 118.8, 46.1, 41.8, 35.5, 30.2, 28.7, 23.2 *m/z* (EI$^+$). Found M+NH_4^+, 526.0796, $C_{18}H_{22}NO_6S_2F_6$ requires 526.0793. Monotriflate **7**: δ_H (270 MHz, $CDCl_3$) 7.26–7.22 (3H, m), 7.06–7.03 (2H, m), 5.73 (1H, dd app. t, *J* 2.2, 2.6 Hz), 2.99 (1H, d, *J* 13.4 Hz), 2.84 (1H, dd, *J* 22.5, 2.6 Hz), 2.79 (1H, d, *J* 13.4 Hz), 2.27 (1H, dd, *J* 22.5, 2.2 Hz), 1.31 (3H, s); δ_C (100 MHz, $CDCl_3$) 216.3, 150.3, 135.3, 129.4, 128.2, 127.0, 118.3, 110.8, 55.5, 42.2, 41.5, 20.6. Found C, 50.5; H, 3.85, $C_{14}H_{13}O_4SF_3$ requires C, 50.3; H, 3.89%. Ditriflate **8**: δ_H (400 MHz, $CDCl_3$) 7.25–7.20 (3H, m), 7.07–7.06 (2H, m), 5.81 (2H, s), 2.97 (2H, s), 1.41 (3H, s); δ_C (100 MHz, $CDCl_3$) 151.9, 134.0, 128.9, 128.0, 127.2, 118.3, 111.9, 54.2, 39.7, 18.5. Found C, 38.4; H, 2.65, $C_{15}H_{12}S_2F_6O_6$ requires C, 38.6; H, 2.6%.

12. For reviews on Suzuki couplings, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

13. For a recent study on the development of low temperature Suzuki couplings employing triflate substrates, see: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

14. Typical coupling procedure. Substrate **2**: Dry THF (1 ml) was added to a mixture of triflate **2** (35.0 mg, 0.1 mmol), Pd(OAc)$_2$ (2.2 mg, 0.01 mmol), triphenylphosphine (5.6 mg, 0.022 mmol) and 4-methoxyphenylboronic acid (19 mg, 0.125 mmol). The solution was stirred under nitrogen for 10 min, KOH (10% aq, 0.2 ml, 0.1 mmol) was then added via syringe and the reaction was stirred at room temperature for 40 min. The mixture was partitioned between water (5 ml) and EtOAc (5 ml). The aqueous layer was extracted (2×2 ml EtOAc). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% DCM/petrol) to give the coupled material as a bright yellow solid, mp 67–68°C (from DCM/hexane); δ_H (400 MHz, $CDCl_3$) 7.24–7.14 (5H, m), 7.09–7.04 (2H, m), 6.90–6.85 (2H, m), 5.81–5.79 (1H, dd app. t, *J* 4.7 and 3.9 Hz), 3.84 (3H, s), 3.14 (1H, d, *J* 13.7 Hz), 2.97 (1H, d, *J* 13.7 Hz), 2.46–2.43 (2H, m), 2.33–2.24 (1H, m), 2.02–1.92 (1H, m), 1.22 (3H, s); δ_C (100 MHz, $CDCl_3$) 214.2, 158.4, 143.8, 137.4, 133.5, 130.2, 129.9, 127.9, 127.8, 126.3, 113.1, 55.3, 53.7, 44.6, 37.3, 24.2, 23.9; *m/z* (EI$^+$) 306.2 (100%, M$^+$). Found M, 306.1617, $C_{21}H_{22}O_2$ requires 306.1620.