Decarboxylative elimination of enol triflates as a general synthesis of acetylenes

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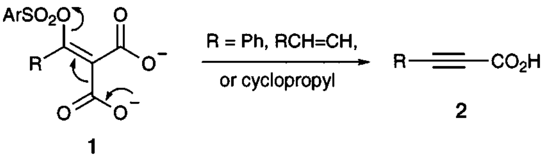
Decarboxylative elimination of a range of enol triflates 11 of β-keto esters gives acetylenes 12.

We established long ago in a series of papers[1,2] that enol arenesulfonates **1** derived from acylmalonates underwent concerted decarboxylative elimination to give acetylenic acids **2** (Scheme 1), provided that the group R was cation-stabilising. Thus the reaction worked if the group R was aryl, vinyl or cyclopropyl, but not if it was alkyl or ethynyl, a severe limitation which deterred us from investigating the synthetic potential of this reaction any further. In the meantime, better leaving groups than arenesulfonate have been developed,[3] and so we have returned to this remarkably mild reaction to see if it could be made into a more general synthesis of acetylenes.

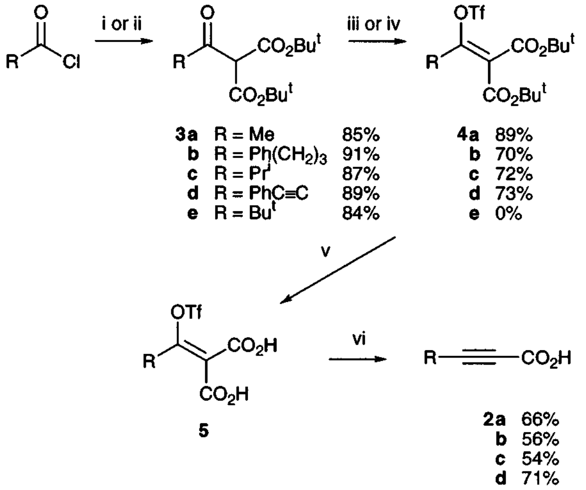


Scheme 1

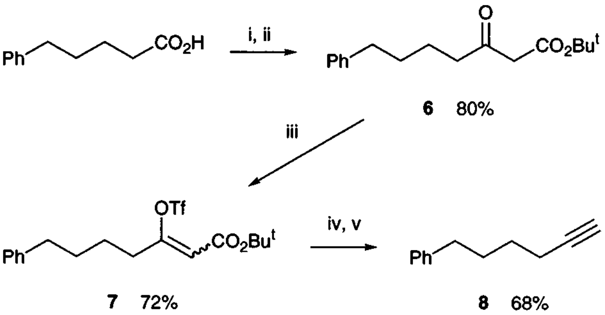
Although we know of no relevant quantitative data for elimination reactions, it is known that 1-adamantyl trifluoromethanesulfonate (triflate) undergoes S_N1 solvolysis 10^5 to 10^6 times faster than the corresponding toluene-*p*-sulfonate (tosylate),[4] and that ethyl triflate undergoes S_N2 solvolysis in AcOH 10^4 faster than ethyl tosylate.[5] We also knew that the rate of the decarboxylative elimination **1** → **2** was sensitive to how good the leaving group was, although not quite to the same extent as an S_N1 reaction. Thus the decarboxylative elimination had a ρ value for *p*-substituted benzenesulfonates of 1.16,[2] whereas the S_N1 reaction of 1-adamantyl arenesulfonates has a ρ value of 1.76.[6] Putting these facts together implied that enol triflates ought to undergo decarboxylative elimination much faster than enol arenesulfonates, and quite probably fast enough to work for those cases that had failed before. We carried out the sequence in Scheme 2 to prepare the enol triflate dicarboxylic acids **5**, and dissolved them in aqueous $NaHCO_3$. They cleanly gave the acetylenic acids **2a**–**d**, having alkyl and ethynyl groups R, showing that the main limitation in our earlier work had been overcome.

With a more general reaction now at our disposal, we investigated whether the second carboxylic acid group was necessary. It had always been possible that the second carboxylate ion, present in all our earlier reactions, had accelerated the decarboxylative elimination by a Coulombic repulsion. We prepared the enol triflate **7** (Scheme 3). On treatment with base this gave the terminal acetylene **8**, showing that the second carboxy group was unnecessary. In this case, K_2CO_3 in refluxing acetone proved to be better than aqueous $NaHCO_3$.

We also prepared a small range of acetylenes **12** and **14** with alkyl groups on both sides (Scheme 4), again with greater success using K_2CO_3 in acetone as the base. We were not successful in our efforts to prepare an enol triflate with branched alkyl groups on both sides of the intended triple bond, neither of the β-keto esters **15** giving an enol triflate, although we were successful with examples having branched chains separately on each side, as in the synthesis of the acetylenes **12c** and **14**. We were also unable to prepare an enol triflate adjacent to a *tert*-butyl group when we treated di-*tert*-butyl pivaloylmalonate **3e** with a variety of bases and Tf_2O.



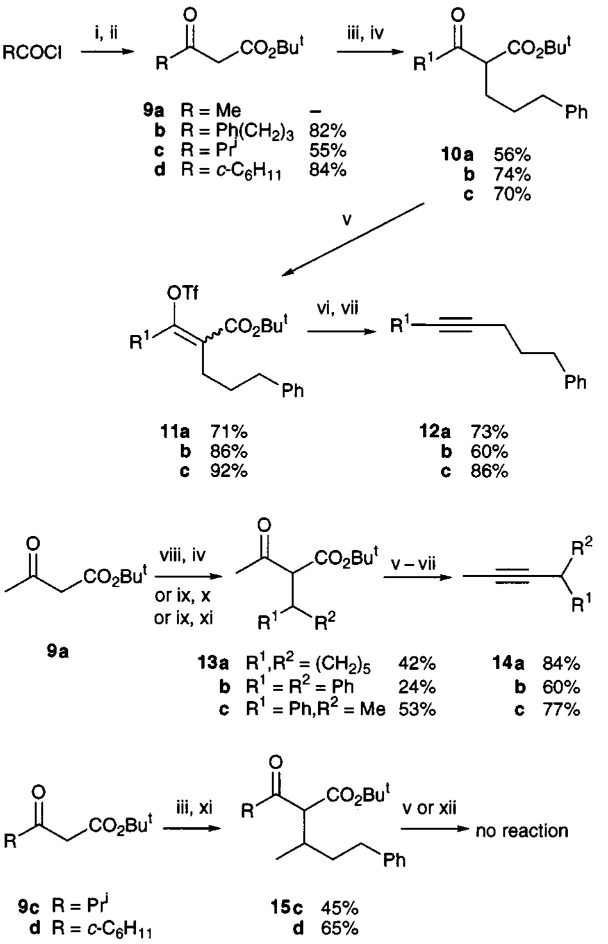
Scheme 2 *Reagents and conditions*: i, $CH_2(CO_2Bu^t)_2$, $Mg(OEt)_2$; ii, $CH_2(CO_2Bu^t)_2$, Et_3N; iii, Tf_2O, Et_3N, CH_2Cl_2, 0 °C → rt, 3 h; iv, NaH, Et_2O, 0 °C, 1 h, then Tf_2O, 0 °C, then rt, 1 h; v, TFA, rt, 30 min; vi, $NaHCO_3$, H_2O, rt, 12 h.



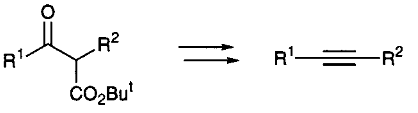
Scheme 3 *Reagents and conditions*: i, carbonyldiimidazole, THF, rt, 1 h; ii, $LiCH_2CO_2Bu^t$, −78 °C, 1 h; iii, NaH, Et_2O, 0 °C, 1 h, then Tf_2O, 0 °C → rt, 1 h; iv, TFA, rt, 30 min; v, K_2CO_3, Me_2CO, reflux, 4 h.

Except for these limitations, we now have a fairly general synthesis of acetylenes based on a β-keto ester system (Scheme 5), with a wide variety of methods for incorporating or attaching the groups R^1 and R^2 on each side of the ketone group,[7] some of which are illustrated by the standard but far from opitimised methods we used in Schemes 2–4. The overall transformation is similar to that achieved by Zard's intriguing reaction,[8] in which β-keto esters are treated successively with hydroxylamine and with $NaNO_2$ and iron(II) sulfate, but the pathway described here is mechanistically more straightforward, and probably less apt to give byproducts.

The following is a representative recipe for the preparation of the enol triflate and for the decarboxylative elimination. The keto-ester **13c** (7 g, 26.7 mmol) in dry Et_2O (50 cm^3) was added to a prewashed suspension of NaH (60% dispersion in mineral oil, 2.13 g, 53.4 mmol) at 0 °C and stirred for 1 h. Tf_2O (6.6 cm^3, 40.0 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C and 1 h at room temperature. The mixture was cooled



Scheme 4 *Reagents and conditions*: i, Meldrum's acid, Py, CH_2Cl_2, 0 °C → rt, 3 h; ii, Bu^tOH, toluene, reflux, 4 h; iii, $Ph(CH_2)_2CHO$, $TiCl_4$, Py, THF, rt, 16 h; iv, H_2, Pd/C, MeOH, rt, 12 h; v, NaH, Et_2O, 0 °C, 1 h, then Tf_2O, 0 °C → rt, 2 h; vi, TFA, rt, 30 min; vii, K_2CO_3, Me_2CO, reflux, 4–5 h; viii, cyclohexanone, $TiCl_4$, Py, CH_2Cl_2, rt, 16 h; ix, PhCHO, c-$C_5H_{10}NH$, EtOH, 5 °C, 14 h; x, Ph_2CuLi, THF, −78 °C, 1 h; xi, Me_2CuLi, THF, −78 °C, 1 h; xii, Tf_2O and several other bases: KH, 2,6-di-*tert*-butylpyridine, *etc.*



Scheme 5

and quenched carefully with water and extracted with Et_2O (2 × 60 cm^3). The extract was washed with saturated $NaHCO_3$ (60 cm^3) and brine (60 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give 3-*tert*-butoxycarbonyl-4-phenylpent-2-en-2-yl trifluoromethanesulfonate (8.94 g, 85%); R_f [EtOAc–light petroleum (bp 40–60 °C), 20 : 80] 0.77; ν_{max} (film)/cm^{-1} 1721 (C=O) and 1602 (Ph); δ_H(250 MHz; $CDCl_3$) 7.3–7.2 (5H, m, Ph), 3.86 (1H, q, *J* 7.3, PhC*H*), 2.1 (3H, s, *Me*C=C), 1.57 (3H, d, *J* 7.2, *Me*CH) and 1.31 (9H, s, Bu^t). The triflate was unstable and had to be used in the next step without further characterisation. The triflate (8.94 g, 22.7 mmol) was stirred in TFA (10 cm^3) for 40 min at room temperature. The excess TFA was removed under reduced pressure to give a light yellow–brown solid, which was dissolved in acetone (50 cm^3). K_2CO_3 (7.3 g, 53.4 mmol) was added and the reaction mixture refluxed for 4 h, cooled, poured into water and extracted with Et_2O. The extract was washed with dilute HCl (50 cm^3), water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40–60 °C)] to give the 4-phenylpent-2-yne[9] **14c** (2.97 g, 77% from the keto ester); R_f [EtOAc–light petroleum (bp 40–60 °C), 10 : 90] 0.85; ν_{max}(film)/cm^{-1} 1450 (Ph); δ_H(250 MHz; $CDCl_3$) 7.4–7.2 (5H, m, Ph), 3.72 (1H, m, PhC*H*), 1.88 (3 H, d, *J* 2.5, *Me*C≡C) and 1.47 (3H, d, *J* 7.2, *Me*CH); δ_C(250 MHz; $CDCl_3$) 144−, 128.4+, 126.8+, 126.4+, 82, 77.5−, 31.9+, 24.6+ and 3.6+ (+ indicates methyl or methine and − indicates methylene or quaternary carbon).

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Notes and references

1 I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 1963, 4771 and 4778; E. J. D. Brown and J. Harley-Mason, *J. Chem. Soc.*, 1966, 1390; I. Fleming and C. R. Owen, *J. Chem. Soc. (C)*, 1971, 2013.

2 I. Fleming and C. R. Owen, *J. Chem. Soc. (B)*, 1971, 1293.

3 T. W. Bentley, in *The Chemistry of Sulphonic Acids, Esters and their Derivatives*, ed. S. Patai and S. Rappoport, Wiley, Chichester, 1991, pp. 671–696.

4 K. Takeuchi, K. Ikai, T. Shibata and A. Tsugeno, *J. Org. Chem.*, 1988, **53**, 2852.

5 A. Streitwieser, Jr., C. L. Wilkins and E. Kiehlmann, *J. Am. Chem. Soc.*, 1968, **90**, 1598. See also: M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott and M. C. Whiting, *J. Chem. Soc., Chem. Commun.*, 1968; 1533; D. N. Kevill and G. M. Lin, *Tetrahedron Lett.*, 1978, 949; J. F. Garrity and J. W. Prodolliet, *Tetrahedron Let.*, 1982, **23**, 417.

6 D. N. Kevill, K. C. Kolwyck, D. M. Shold and C.-B. Kim, *J. Am. Chem. Soc.*, 1973, **95**, 1065.

7 S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto and V. Zanirato, *Chem. Rev.*, 1995, **95**, 1065.

8 J. Boivin, L. ElKaim, P. G. Ferro and S. Z. Zard, *Tetrahedron Lett.*, 1991, **32**, 5321; J. Boivin, S. Huppé and S. Z. Zard, *Tetrahedron Lett.*, 1995, **36**, 5737; J. Boivin, S. Huppé and S. Z. Zard, *Tetrahedron Let.*, 1996, **37**, 8735.

9 J. C. Gilbert, D. H. Giamalva and U. Weerasooriya, *J. Org. Chem.*, 1983, **48**, 5251.

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