View Article Online / Journal Homepage / Table of Contents for this issue

Double decarboxylative Claisen rearrangement reactions: microwave-assisted *de novo* synthesis of pyridines†

Donald Craig,*[a] Federica Paina[a] and Stephen C. Smith[b]

Received (in Cambridge, UK) 26th March 2008, Accepted 15th April 2008
First published as an Advance Article on the web 14th May 2008
DOI: 10.1039/b805078c

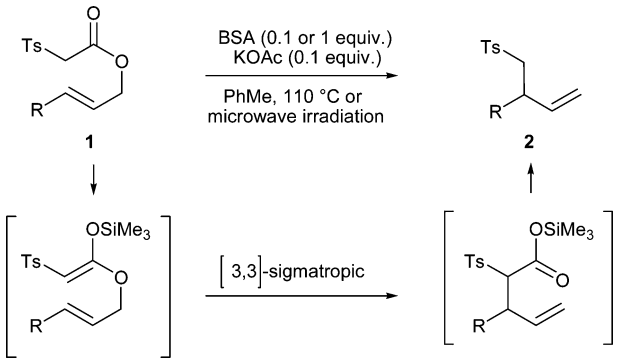
Published on 14 May 2008. Downloaded by The University of British Columbia Library on 30/10/2014 01:21:24.

Microwave-assisted double decarboxylative Claisen rearrangement of bis(allyl) 2-tosylmalonates provides substituted 1,6-heptadienes, which may be alkylated, and then converted into pyridines by ozonolysis followed by reaction with ammonia generated *in situ* under microwave conditions.

Since its discovery over 35 years ago, the Ireland–Claisen rearrangement[1] has become established as a strategy-level transformation for the stereoselective and regiospecific formation of C–C bonds. It has emerged as the Claisen rearrangement variant of choice because of the ready availability of the allylic ester substrates, and the mildness of the rearrangement conditions.[2] In recent years, we have been developing a catalysed version of the Ireland–Claisen rearrangement: the decarboxylative Claisen rearrangement (dCr) reaction involves exposure of allylic tosylacetates **1** to *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate under relatively mild thermal conditions, and provides homoallylic sulfones **2** in good to excellent yields (Scheme 1).[3–7] In many instances BSA and KOAc may be used in sub-stoichiometric amounts.[8,9]

It occurred to us that two sequential dCr reactions might take place in one pot on exposure of analogous bis(allyl) 2-tosylmalonates to the BSA–KOAc reagent combination. The products of these transformations would be substituted 1,6-heptadienes, which would be converted into pyridines by an ozonolysis–ammonolysis sequence developed previously in our laboratory.[10] In this earlier work, the position of pyridine substitution had been constrained by the use of enolate-mediated and allylpalladium-based methods for the *C*-allylation of tosylacetic esters. In contrast, use of a double dCr reaction strategy in principle would enable access to pyridines substituted at C-3 and/or C-5 because of the regiospecific nature of the allylation process taking place in the rearrangement step (Scheme 2).

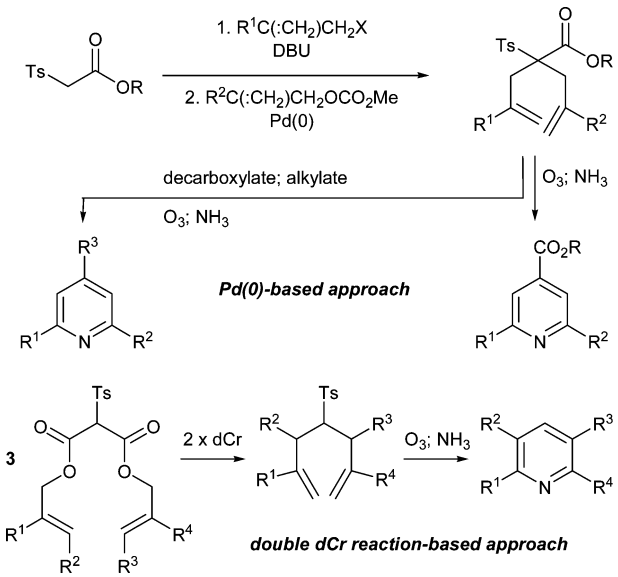
The syntheses of substrates **3** required for this study were carried out using a modification[11] of our published[4] procedure.[12] Previous investigations had shown that the first rearrangement of bis(allyl) 2-tosylmalonates takes place at ambient temperature, and that the mono-rearranged products



Scheme 1 Decarboxylative Claisen rearrangement reaction.

undergo the second dCr reaction much less readily.[13] This work had shown that substrate **3a** could selectively be converted into the mono-rearranged product **5a** and therefore **3a** was used to optimise the one-pot, double-rearrangement (Scheme 3, Table 1).

Initially a mixture of **3a**, BSA (1.0 equiv.) and KOAc (0.1 equiv.) was subjected to conventional heating in toluene under reflux for several hours (entry 1). Progressive decomposition of BSA and starting material was observed, while only trace amounts of **4a** were detected, with predominant formation of the mono-rearrangement product **5a**. When the reaction was carried out under microwave conditions in dichloromethane (entry 2) only the product of mono-rearrangement could be isolated (47%) alongside unreacted starting material **3a** (42%). Use of a better microwave absorber such as



Scheme 2 Synthesis of pyridines using 4-tosyl-1,6-heptadienes.

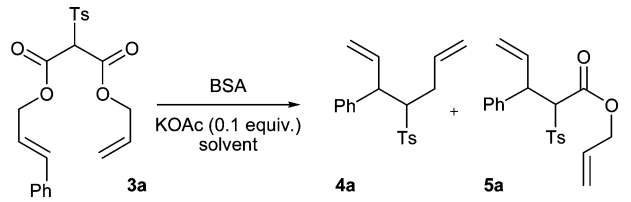
[a] *Department of Chemistry, Imperial College London, South Kensington Campus, London, UK SW7 2AZ. E-mail: d.craig@imperial.ac.uk; Fax: +44 (0)20 7594 5868; Tel: +44 (0)20 7594 5771*
[b] *Syngenta, Crop Protection Research Chemistry, Jealott's Hill International Research Centre, Bracknell, Berkshire, UK RG42 6EY*

† Electronic supplementary information (ESI) available: Experimental procedures and full characterisation of compounds **3b–f**, **4a–f**, **5b,d**, **6a–c**, 3-phenyl-4-(*p*-toluenesulfonyl)heptane-2,6-dione, and **7a–i**. See DOI: 10.1039/b805078c

 This journal is © The Royal Society of Chemistry 2008

View Article Online

Published on 14 May 2008. Downloaded by The University of British Columbia Library on 30/10/2014 01:21:24.



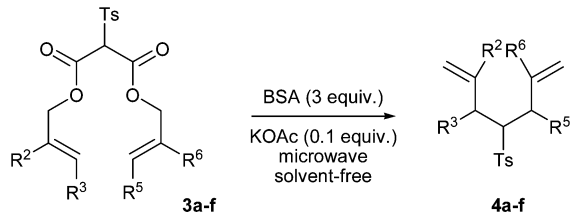
Scheme 3 Double dCr reaction of **3a**.

1,2-dichlorobenzene[14] (entry 3) resulted in the formation of **4a** as the major product. Optimisation of these reaction conditions led to the isolation of diene **4a** in 86% yield as a 1 : 1 mixture of diastereoisomers when the reaction was carried out *in the absence of solvent* (entry 5). This transformation could be performed on several-gram scales without any loss in efficiency, and the solvent-free procedure was adopted as the method of choice.

Further experimentation showed the use of microwave acceleration to be essential for the realisation of efficient double dCr reactions (Scheme 4, Table 2). In some cases, reactions were stopped prior to the complete consumption of malonate, in order to minimise contamination of the dienes with decomposition products (entries 1 and 3). It was found that carrying out irradiation in a number of short pulses rather than over longer, continuous periods gave higher and more reproducible yields.[14,15] The rate-enhancing effect of a phenyl group *versus* a hydrogen atom in the R^3 position[13] was highlighted by the significantly harsher conditions required to effect transformation of substrate **3e** (entry 4). All diene products were formed as mixtures of two (R^3 or R^5 = H) or four (R^3, $R^5 \neq$ H) diastereoisomers.

With a route to di-, tri- and tetrasubstituted 1,6-heptadienes established, it occurred to us that incorporation of a fifth substituent might be possible by alkylation α- to the tosyl group (Scheme 5).[10,17] This would allow the synthesis of pyridines substituted additionally at the 4-position. While exposure of **4a** to *n*BuLi followed by 1-iodononane provided diene **6a** in good yield, significantly lower yields were obtained for more highly substituted substrates. The disubstituted heptadiene **4b** gave trisubstituted analogue **6b** in only 40% yield under similar conditions, and benzylation of **4b** using $PhCH_2Br$ gave a 56% yield of **6c** (Table 3). Dienes which were substituted additionally at the 6-position failed to yield any 4-substituted products using this approach.

Dienes **4** and **6** were converted into pyridines by ozonolysis with mild reductive work-up, followed by exposure of the crude 1,5-dicarbonyl products to excess NH_4HCO_3[18] in methanol with microwave irradiation for 10 min at 100 °C (Scheme 6). Longer reaction times resulted in lower yields,

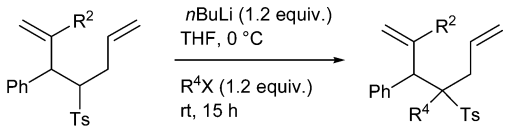


Scheme 4 Double dCr reactions of bis(allylic) 2-tosylmalonates **3b–f**.

Table 2 Double dCr reactions of bis(allylic) 2-tosylmalonates **3b–f**

Entry	Substrate	R^2	R^3	R^5	R^6	Yield of **4** (%)[a]	Reaction conditions
1	**3b**	Me	Ph	H	H	**4b**: 77[b]	4 × 3 min @ 200 °C
2	**3c**	Me	Ph	H	Me	**4c**: 70	2 × 3 min @ 240 °C
3	**3d**	Me	Ph	Me	Me	**4d**: 56[c]	6 × 1 min @ 180 °C
4	**3e**	Me	H	$-(CH_2)_4-$		**4e**: 62	4 × 3 min @ 220 °C; 3 × 2 min @ 240 °C
5	**3f**	H	Ph	$-(CH_2)_4-$		**4f**: 58	6 × 1 min @ 190 °C

[a] Isolated yield. [b] Mono-rearranged product was isolated also (7%).[16] [c] Mono-rearranged products were isolated also (23%).



Scheme 5 4-Alkylation of 1,6-heptadienes **4a**,**b**.

Table 3 4-Alkylation of 1,6-heptadienes **4a**,**b**

Substrate	R^2	R^4X	Product	Yield (%)[a]
4a	H	$nC_9H_{19}I$	**6a**	86
4b	Me	$nC_9H_{19}I$	**6b**	40
4b	Me	$PhCH_2Br$	**6c**	56

[a] Isolated yield.

particularly when the intermediate dicarbonyl compounds contained aldehyde groups (R^2 and/or R^6 = H). The results are summarised in Table 4.

For one substrate the efficiency of the pyridine formation step on its own was evaluated by ammonolysis of 3-phenyl-4-tosylheptane-2,6-dione, obtained in 72% isolated yield by ozonolysis of **4c**. The diketone was converted into pyridine **7c** in 98% yield, both by using ammonia in methanol (rt, overnight)[10] and with NH_4HCO_3 in methanol (microwave, 100 °C, 10 min) as the source of ammonia.

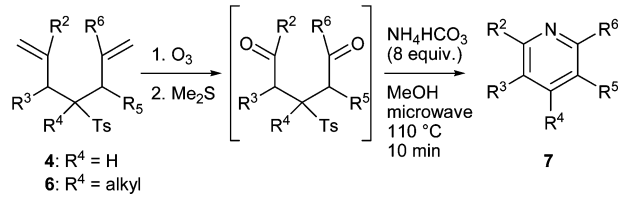
Table 1 Optimisation of double dCr reaction of **3a**

Entry	Solvent	Equiv. BSA	Reaction conditions	Yield of **4a**[a] (%)	By-product
1	PhMe	6	Reflux, 53 h	0%	**5a**[b]
2	CH_2Cl_2	1	Microwave, 110 °C, 15 min	0%	**5a**[c] (47%)
3	$1,2\text{-}Cl_2C_6H_4$	1	Microwave, 180 °C, 5 min	66%	—
4	$Cl(CH_2)_2Cl$	1	Microwave, 170 °C, 15 min	50%	—
5	None	3[d]	Microwave, 170 °C, 4 min	86%	—

[a] Isolated yield. [b] Compound **5a** and unidentified decomposition products were isolated, together with unreacted starting material. [c] Unreacted starting material was also isolated (42%). [d] The reaction was carried out under solvent-free conditions.

View Article Online

Published on 14 May 2008. Downloaded by The University of British Columbia Library on 30/10/2014 01:21:24.



Scheme 6 Formation of pyridines **7**.

Table 4 Formation of pyridines **7** from 4-tosyl-1,6-heptadienes

Entry	Diene	R^2	R^3	R^4	R^5	R^6	Yield of **7** (%)[a]
1	**4a**	H	Ph	H	H	H	**7a**: 53
2	**4b**	Me	Ph	H	H	H	**7b**: 86
3	**4c**	Me	Ph	H	H	Me	**7c**: 73
4	**4d**	Me	Ph	H	Me	Me	**7d**: 81
5	**4e**	Me	H	H	$-(CH_2)_4-$		**7e**: 37
6	**4f**	H	Ph	H	$-(CH_2)_4-$		**7f**: 63
7	**6a**	H	Ph	nC_9H_{19}	H	H	**7g**: 98
8	**6b**	Me	Ph	nC_9H_{19}	H	H	**7h**: 100
9	**6c**	Me	Ph	$PhCH_2$	H	H	**7i**: 75

[a] Isolated yield based on **4** or **6**.

In summary, we have developed a new, microwave-assisted method for the synthesis of substituted pyridines using the double dCr reaction as a key step. Ongoing studies are directed towards expanding the scope of this chemistry to accommodate the synthesis of bicyclic analogues, and of chiral pyridines possessing benzylic stereocentres. The results of these investigations will be reported in due course.

This research was supported by EPSRC (responsive mode grant GR/T10268) and Syngenta (supported DTA studentship to F.P.).

Notes and references

1. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897 For reviews of the Ireland–Claisen rearrangement, see: (*a*) S. Pereira and M. Srebnik, *Aldrichimica Acta*, 1993, **26**, 17; (*b*) Y. Chai, S. Hong, H. A. Lindsay, C. McFarland and M. McIntosh, *Tetrahedron*, 2002, **58**, 2905.
2. For a recent review of the Claisen rearrangement, see: A. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.
3. D. Bourgeois, D. Craig, N. P. King and D. M. Mountford, *Angew. Chem., Int. Ed.*, 2005, **44**, 618.
4. D. Craig and F. Grellepois, *Org. Lett.*, 2005, **7**, 463.
5. D. Craig, F. Grellepois and A. J. P. White, *J. Org. Chem.*, 2005, **70**, 6827.
6. D. Craig, N. P King, J. T. Kley and D. M. Mountford, *Synthesis*, 2005, 3279.
7. D. Bourgeois, D. Craig, F. Grellepois, D. M. Mountford and A. J. W. Stewart, *Tetrahedron*, 2006, **62**, 483.
8. For the first report of Ireland–Claisen rearrangement of an allylic α-phenylsulfonylacetate followed by decarboxylation, which took place in a separate step, see: A. H. Davidson, N. Eggleton and I. H. Wallace, *J. Chem. Soc., Chem. Commun.*, 1991, 378.
9. For a report of the mechanistically distinct Carroll rearrangement of an allylic α-phenylsulfonyl ester under strongly basic conditions, see: M. A. Hatcher and G. H. Posner, *Tetrahedron Lett.*, 2002, **43**, 5009.
10. D. Craig and G. D. Henry, *Tetrahedron Lett.*, 2005, **46**, 2559.
11. The previously reported (ref. 4) tosylation of methyl allylic malonates required the use of 4.5 equiv. substrate, 4.0 equiv. *t*BuOK and 1.0 equivalent of tosyl fluoride in DMSO (2 M solution). In this study, the ratios of substrate:*t*BuOK:TsF were improved to 2 : 2 : 1 for the synthesis of diallylic tosylmalonates **3a–f** (see ESI†).
12. For recent reports of sulfonylation α- to carbonyl groups mediated by enols/enolates, see: (*a*) A. S. Kende and J. S. Mendoza, *J. Org. Chem.*, 1990, **55**, 1125; (*b*) V. P Sandanayaka, A. Zask, A. M. Venkatesan and J. Baker, *Tetrahedron Lett.*, 2001, **42**, 4605; (*c*) A. R. Katritzky, A. A. A. Abdel-Fattah, A. V. Vakulenko and H. Tao, *J. Org. Chem.*, 2005, **70**, 9191; (*d*) M. Kreis, M. Nieger and S. Braese, *J. Organomet. Chem.*, 2006, **691**, 2171; (*e*) D. Kumar, S. Sundaree, V. S. Rao and R. S. Varma, *Tetrahedron Lett.*, 2006, **47**, 4197; (*f*) R. Kumar, S. Saingar, P. Joshi and Y. C. Joshi, *Indian J. Heterocycl. Chem.*, 2005, **14**, 353; (*g*) A. M. Venkatesan, J. M. Davis, G. T. Grosu, J. Baker, A. Zask, J. I. Levin, J. Ellingboe, J. S. Skotnicki, J. F. DiJoseph, A. Sung, G. Jin, W. Xu, D. J. McCarthy and D. Barone, *J. Med. Chem.*, 2004, **47**, 6255; (*h*) J. K. Bin, J. S. Lee and K. Kim, *Org. Lett.*, 2004, **6**, 4297.
13. D. Craig, M. I. Lansdell and S. E. Lewis, *Tetrahedron Lett.*, 2007, **48**, 7861.
14. T. Durand-Reville, L. B. Gobbi, B. L. Gray, S. V. Ley and J. S. Scott, *Org. Lett.*, 2002, **4**, 3847.
15. J. Siu, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2004, 160.
16. The mono-rearranged product was that of rearrangement of the cinnamyl group.
17. For recent reports of sulfone alkylation α- to a tosyl group, see: (*a*) M. H. Weston, K. Nakajima, M. Parvez and T. G. Back, *Chem. Commun.*, 2006, 3903; (*b*) H. Comas and E. Pandolfi, *Synthesis*, 2004, 2493.
18. J. Lu, Y.-J. Bai, B.-Q. Yang and H.-R. Ma, *Chin. J. Org. Chem.*, 2000, **20**, 514.

 This journal is © The Royal Society of Chemistry 2008