

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

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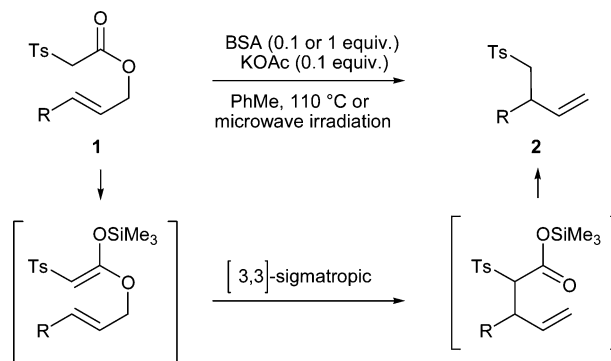
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Microwave-assisted double decarboxylative Claisen rearrangement of bis(allyl) 2-tosylmalonates provides substituted 1,6-heptadienes, which may be alkylated, and then converted into pyridines by ozonolysis followed by reaction with ammonia generated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

Since its discovery over 35 years ago, the Ireland–Claisen rearrangement¹ has become established as a strategy-level transformation for the stereoselective and regioselective 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 regioselective nature of the allylation process taking place in the rearrangement step (Scheme 2).

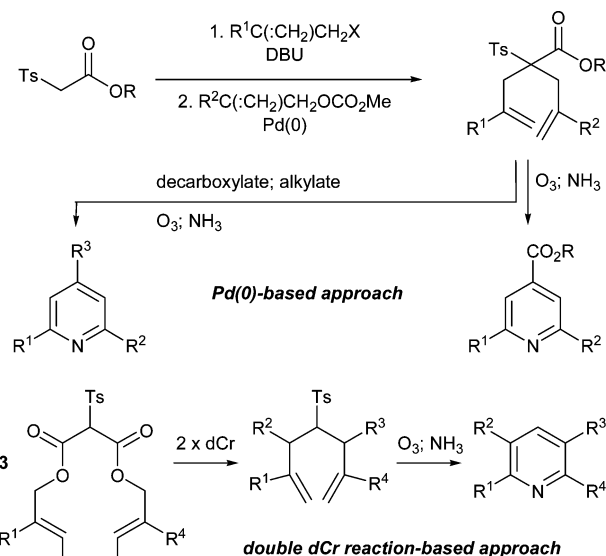
The syntheses of substrates **3** required for this study were carried out using a modification¹¹ of our published⁴ procedure.¹² Previous investigations had shown that the first rearrangement of bis(allyl) 2-tosylmalonates takes place at ambient temperature, and that the mono-rearranged products



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



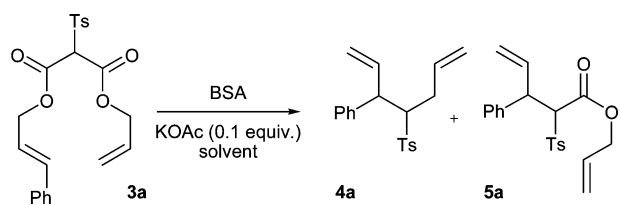
Scheme 2 Synthesis of pyridines using 4-tosyl-1,6-heptadienes.

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† 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



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

1,2-dichlorobenzene¹⁴ (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 R³ position¹³ 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 (R³ or R⁵ = H) or four (R³, R⁵ ≠ H) diastereoisomers.

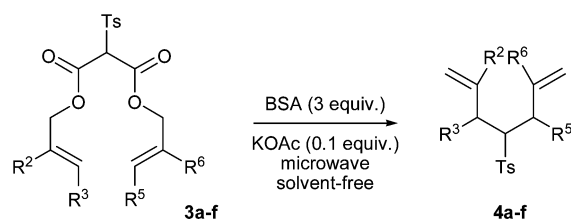
With a route to di-, tri- and tetrasubstituted 1,6-heptadienes established, it occurred to us that incorporation of a fifth substituent might be possible by alkylation α - to the tosyl group (Scheme 5).^{10,17} This would allow the synthesis of pyridines substituted additionally at the 4-position. While 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 PhCH₂Br 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 NH₄HCO₃¹⁸ in methanol with microwave irradiation for 10 min at 100 °C (Scheme 6). Longer reaction times resulted in lower yields,

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 ₂ Cl ₂	1	Microwave, 110 °C, 15 min	0%	5a ^c (47%)
3	1,2-Cl ₂ C ₆ H ₄	1	Microwave, 180 °C, 5 min	66%	—
4	Cl(CH ₂) ₂ Cl	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.

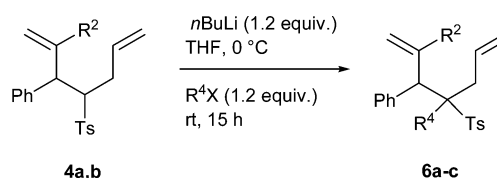


Scheme 4 Double dCr reactions of bis(allylic) 2-tosylmalonates **3b–f**.

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**.

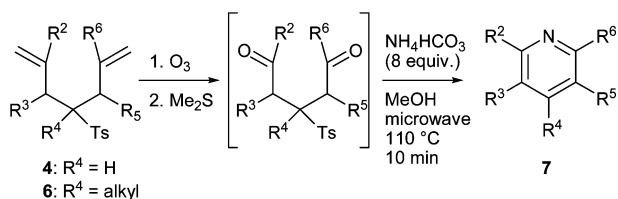
Table 3 4-Alkylation of 1,6-heptadienes **4a,b**

Substrate	R ²	R ⁴ X	Product	Yield (%) ^a
4a	H	<i>n</i> C ₉ H ₁₉ I	6a	86
4b	Me	<i>n</i> C ₉ H ₁₉ I	6b	40
4b	Me	PhCH ₂ Br	6c	56

^a Isolated yield.

particularly when the intermediate dicarbonyl compounds contained aldehyde groups (R² and/or R⁶ = 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 NH₄HCO₃ in methanol (microwave, 100 °C, 10 min) as the source of ammonia.



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 -	H	7e : 37
6	4f	H	Ph	H	-(CH ₂) ₄ -	H	7f : 63
7	6a	H	Ph	nC ₉ H ₁₉	H	H	7g : 98
8	6b	Me	Ph	nC ₉ H 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.

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