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Sulfone-mediated synthesis of polysubstituted pyridines

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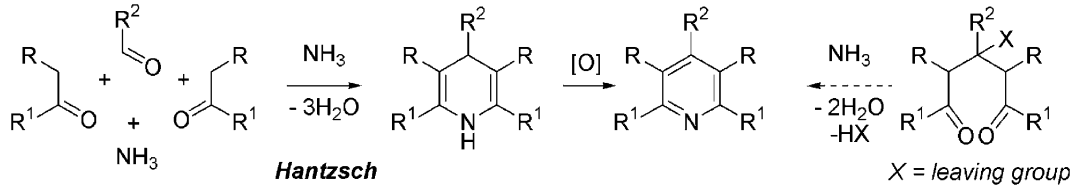
Abstract—Base-mediated and/or palladium(0)-catalysed bis(allylation) of alkyl 2-(tolylsulfonyl)acetates gives 1,6-dienes, which upon ozonolytic cleavage of the double bonds and ammonolysis give 2,6-disubstituted pyridine-4-carboxylic esters. Decarboxylation of one of the 1,6-diene intermediates followed by deprotonation–alkylation and ozonolysis–ammonolysis gives a 2,4,6-trisubstituted pyridine.

Pyridines are ubiquitous, important structural motifs in a wide range of biologically important compounds, and the development of efficient, versatile methods for their synthesis remains a significant goal.[1] We became interested in identifying new ways to synthesise pyridines in which an arylsulfonyl group would serve both to facilitate C–C bond-forming reactions and as a leaving group in the final, aromatisation step. We recognised that if the key 1,5-dicarbonyl intermediates in the classical Hantzsch strategy[2] could be made in a modified way by incorporation of a leaving group at C3, rather than at C2 as in the Kröhnke synthesis,[3] then the following condensation with ammonia in the oxidation step would no longer be necessary (Scheme 1). This letter describes the realisation of these plans.

It occurred to us that the 3-substituted-1,5-dicarbonyl compounds required for our study might be accessible by oxidative cleavage of the double bonds in 1,6-dienes bearing a leaving group at the 4-position. This approach was particularly attractive because of the functional group symmetry present in such compounds, which pointed towards routes involving sequential bis(allylation) of a one-carbon unit bearing the leaving group. It seemed likely that 2-(tolylsulfonyl)acetic esters would combine the required nucleofugality of the arylsulfonyl group[4,5] with facile conjugate base generation.[6] Also, there would be the option to retain or dispose of the carboxyl group at the 1,6-diene stage, opening the way to additional, non-carboxylic substitution at the 4-position.

Initial studies involved mono-allylation of methyl[7,8] or ethyl[9] 2-(tolylsulfonyl)acetate **1a**,**b** to provide **2** by exposure to excess base (2 equiv unless stated otherwise) followed by addition of allylic chlorides, bromides or tosylates (1 equiv unless stated otherwise), usually in the presence of sub-stoichiometric amounts (0.1 equiv) of tetra-*n*-butylammonium iodide. Extensive experimentation identified DBU–DMF as the best base–solvent combination for the majority of cases, in terms of both operational simplicity and yield, with minimal formation of bis(allylated) material **3** observed even with excess (2–8 equiv) base. Incorporation of the second



Scheme 1.

Keywords: Allylation; 1,6-Dienes; Palladium-catalysed; Pyridines; Sulfone.
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allylic substituent using these conditions proved to be more difficult, an observation consistent with the clean mono-allylation described above. Attention was turned to palladium-catalysed allylation reactions, and eventually it was established that room temperature treatment of **2** with NaH in THF followed by addition of allylic chlorides, bromides or tosylates[10] in the presence of sub-stoichiometric quantities of $[Pd(PPh_3)_4]$ resulted in clean, and in many cases near-quantitative conversion into the bis(allylated) products **3**. These conditions could be employed for efficient, one-pot symmetrical bis(allylation) reactions also; **3j** ($R^1 = R^2 = Ph$) was made directly from **1a** and 2-phenylallyl tosylate in 80% yield. Potassium *tert*-butoxide was generally less effective than NaH in these transformations. Finally, it was found in the single example attempted that sequential mono-allylation and unsymmetrical bis(allylation) could be achieved in high yield (96%) by the one-pot, stepwise combination of **1a** with methallyl methyl carbonate followed by allyl methyl carbonate in the presence of $Pd_2(dba)_3$ (0.05 equiv) and PPh_3 (0.5 equiv) in THF at 60 °C,[11] giving 1,6-diene **3e**. Related conditions, in which PPh_3 was replaced by $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$[12] were effective for the one-step synthesis of **3k** ($R^1 = R^2 = Me$) from **1a** using bis(methallyl) carbonate alone. The allylation reactions of **1** are depicted in Schemes 2 and 3 and the results collected in Tables 1 and 2.

With robust syntheses of the required 1,6-dienes **3** in hand, attention was turned to the ozonolysis–ammonolysis sequence necessary to access pyridines. It was found that **3** could be converted into the intermediate 3,3-disubstituted-1,5-dicarbonyl compounds **4** in moderate to good yields by brief ozonolysis in $MeOH–CH_2Cl_2$ at 0 °C, followed by mild, reductive work-up using triphenylphosphine. In general, compounds **4** were found to be unstable over several hours at room temperature but could be stored in a freezer for limited periods. Conversion of **4** into pyridines **5** was most effectively carried out by treatment of dichloromethane solutions of the dicarbonyl compounds with 2 M ethanolic ammonia[13] at ambient temperature overnight followed by straightforward purification either by passage through SCX2 cartridges[14] or by conventional flash column chromatography on silica gel. Compounds **4a** and **j** failed to give viable yields of **5**; in these cases stable intermediates **6** and **7** respectively were isolated from the reaction mixtures. For a number of examples (**3b**,**d**,**e**,**k**), the ozonolysis and ammonolysis steps could be carried out in one-

Table 1. Mono-allylation reactions of tosylacetic esters **1**

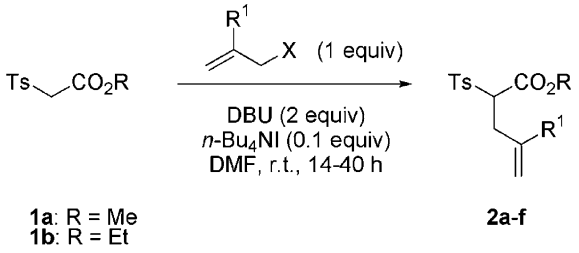
Entry	R	R^1	X	Product (% yield)
1	Me	H	Br	**2a** (70)[a]
2	Me	Me	Cl	**2b** (77)
3	Et	Me	Cl	**2c** (93)[b,c]
4	Me	Et	OTs	**2d** (72)[c]
5	Et	Et	OTs	**2e** (99)[d,e]
6	Me	Ph	OTs	**2f** (84)[e,f]

[a] Bis(allylated) product (5%) was also obtained.
[b] Toluene, instead of DMF, was used as solvent.
[c] 1 equiv of *n*-Bu_4NI was used.
[d] The reaction was carried out in the absence of *n*-Bu_4NI; 16 equiv of allylic tosylate was used.
[e] 8 equiv of DBU was used.
[f] 5 equiv of allylic tosylate was used.

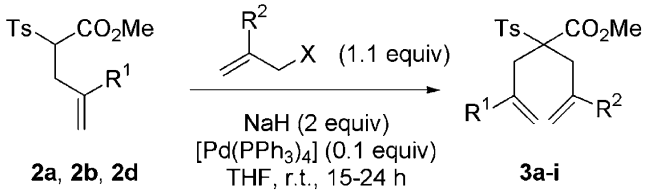
Table 2. Allylation reactions of mono-allylated tosylacetic esters **2**

Entry	Substrate	R^1	R^2	X	Product (% yield)
1	**2a**	H	H	Br	**3a** (99)
2	**2a**	H	Et	Cl	**3b** (54)
3	**2a**	H	Ph	Cl	**3c** (62)
4	**2a**	H	$n\text{-}C_8H_{17}$	OTs	**3d** (99)[a,b]
5	**2b**	Me	H	Br	**3e** (95)
6	**2b**	Me	Ph	OTs	**3f** (99)
7	**2d**	Et	Me	Cl	**3g** (99)[c]
8	**2d**	Et	Et	OTs	**3h** (99)
9	**2d**	Et	Ph	OTs	**3i** (96)

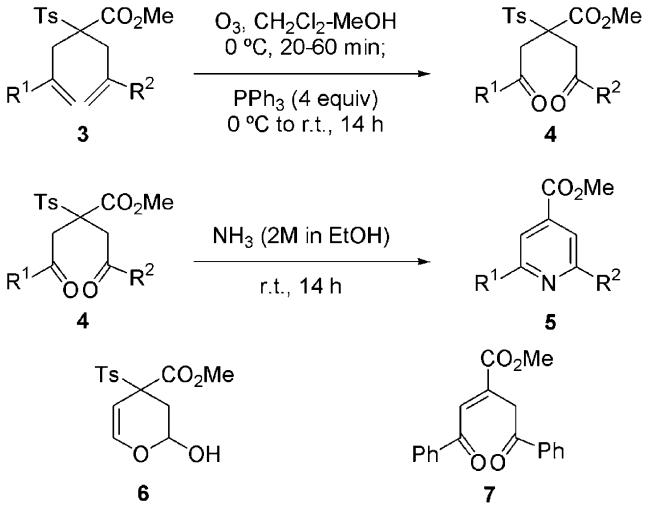
[a] Allylic tosylate (1.3 equiv) was used.
[b] $[Pd(PPh_3)_4]$ (0.05 equiv) was used.
[c] 2 equiv of methallyl chloride was used.



Scheme 2.



Scheme 3.

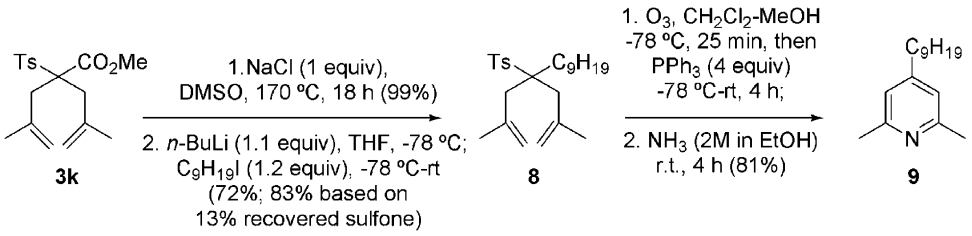


Scheme 4.

Table 3. Ozonolysis–ammonolysis reactions of bis(allylated) tosylacetic esters **3**

Entry	Ozonolysis substrate	R^1	R^2	Ozonolysis product (% yield)	Ammonolysis product (% yield)	One-pot ozonolysis–ammonolysis product (% yield)
1	**3a**	H	H	**4a** (76)	**5a** (7)	—
2	**3b**	H	Et	—	—	**5b** (42)
3	**3c**	H	Ph	**4c** (77)	**5c** (82)	—
4	**3d**	H	n-C_8H_{17}	—	—	**5d** (56)
5	**3e**	H	Me	—	—	**5e** (58)
6	**3f**	Me	Ph	**4f** (57)	**5f** (80)	—
7	**3g**	Me	Et	**4g** (57)	**5g** (90)	—
8	**3h**	Et	Et	**4h** (80)	**5h** (97)	—
9	**3i**	Et	Ph	**4i** (74)	**5i** (83)	—
10	**3j**	Ph	Ph	**4j** (76)	**5j** (13)	—
11	**3k**	Me	Me	**4k** (86)	**5k** (83)[a]	**5k** (83)

[a] The ammonolysis was carried out at −33 °C → rt.



Scheme 5.

pot; in these cases the ozonolysis reactions were conducted at −78 °C and worked up by PPh_3 treatment prior to addition of ethanolic ammonia and warming to room temperature. The pyridine-forming reactions are depicted in Scheme 4 and the results summarised in Table 3.

The final part of this study was devoted to evaluating the efficiency of the decarboxylation–alkylation of intermediates **3** in order to access 2,4,6-trisubstituted pyridines without the carboxylic functional group at C4. To this end, 1,6-diene **3k** was subjected to decarboxylation under standard Krapcho conditions[15] to give the corresponding sulfone in virtually quantitative yield. Treatment of this with n-BuLi followed by 1-iodononane gave the corresponding 4-substituted compound **8** in good yield, though these reactions invariably failed to reach completion. Treatment of **8** under the now standard one-pot ozonolysis–ammonolysis conditions gave 2,6-dimethyl-4-nonylpyridine **9** in high yield (Scheme 5).

In conclusion, we have uncovered a new synthesis of pyridines from simple precursors which are assembled in a modular fashion from readily available starting materials.[16] Ongoing studies are directed towards the synthesis of pyridines possessing substitution patterns not readily accessible using the direct allylation methods described herein, including natural products. The results of these studies will be reported shortly.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.105.

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13. Purchased from Aldrich Chemical Co. and used as supplied.
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16. Typical procedure for mono-allylation of compound **1**: a solution of 2-methylenebutyl tosylate (2.11 g, 8.8 mmol, 1.0 equiv) in DMF (5 mL) was added dropwise over 10 min to a stirred solution of methyl tosylacetate **1a** (2.00 g, 8.8 mmol, 1.0 equiv), *n*-Bu_4NI (0.486 g, 8.8 mmol, 1.0 equiv) and DBU (2.66 mL, 2.71 g, 17.6 mmol, 2.0 equiv) in DMF (25 mL), causing the solution to turn brown and to evolve heat. After 18 h at rt, CH_2Cl_2 (100 mL) was added and the mixture was washed with aqueous HCl (2 M; 75 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were then washed with water (200 mL), separated and dried ($MgSO_4$). Concentration under reduced pressure and chromatography gave methyl 4-methylene-2-(toluene-4-sulfonyl)hexanoate **2d** (1.87 g, 72%) as a yellow oil which later crystallised as a colourless crystalline solid; mp 57–58 °C (EtOAc–petrol).
    Typical procedure for allylation of compound **2**: to a colourless solution of ester **2d** (501 mg, 1.69 mmol, 1.0 equiv) and 2-methylenebutyl tosylate (447 mg, 1.86 mmol, 1.1 equiv) in dry THF (5 mL) was added sodium hydride (60% dispersion in mineral oil, 0.214 g, 5.35 mmol, 2.0 equiv) under a nitrogen atmosphere with stirring at rt, turning the reaction mixture a yellow colour with a frothy consistency. To this solution was added a yellow solution of tetrakis(triphenylphosphine)palladium(0), made from the addition of triphenylphosphine (221 mg, 0.85 mmol, 0.5 equiv) to a solution of tris(dibenzylideneacetone)dipalladium(0) (78 mg, 0.09 mmol, 0.05 equiv) in dry THF (3 mL) under a nitrogen atmosphere at rt followed by stirring for 10 min. After 20 h of stirring at rt saturated aqueous NH_4Cl (15 mL) and Et_2O (15 mL) were added, turning the solution a darker brown colour. The aqueous layer was separated and extracted with Et_2O (2×20 mL). The combined organic layers were washed with water (1×25 mL), brine (1×25 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography gave methyl 4-methylene-2-(2-methylenebutyl)-2-(toluene-4-sulfonyl)hexanoate **3h** (615 mg, 99%) as a colourless crystalline solid; mp 62–63 °C ($CHCl_3$).
    Typical procedure for ozonolysis of compound **3**: to a stirred solution of compound **3h** (408 mg, 1.12 mmol, 1 equiv) in CH_2Cl_2 (36 mL) and MeOH (4 mL) at 0 °C was bubbled O_2 (10 min), then O_3 (20 min) until the solution turned blue, followed by O_2 (10 min). PPh_3 (881 mg, 3.36 mmol, 3 equiv) was added and the solution was stirred for 1 h at 0 °C followed by 18 h at rt. Concentration under reduced pressure and chromatography (33% EtOAc–petrol) gave methyl 4-oxo-2-(2-oxobutyl)-2-(toluene-4-sulfonyl)hexanoate **4h** (0.329 g, 80%) as a colourless crystalline solid; mp 57–59 °C (EtOAc).
    Typical procedure for conversion of 1,5-dicarbonyl compounds **4** into pyridines **5**: to a solution of diketone **4h** (69 mg, 0.179 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at room temperature was added NH_3 (2 M in ethanol, 1.5 mL), turning the solution from colourless to yellow. After stirring for 16 h, TLC showed complete consumption of the starting material and then CH_2Cl_2 (5 mL) was added. The reaction mixture was washed with H_2O (5 mL), the aqueous layer was extracted with CH_2Cl_2 (3 mL) and the combined organic layers were dried ($MgSO_4$). Concentration under reduced pressure and chromatography (33% EtOAc–petrol) gave methyl 2,6-diethylpyridine-4-carboxylate **5h** (0.051 g, 97%) as a yellow oil.