Pergamon

Tetrahedron Letters 41 (2000) 1543–1547

TETRAHEDRON
LETTERS

Tosylates in palladium-catalysed coupling reactions. Application to the synthesis of arylcoumarin inhibitors of gyrase B

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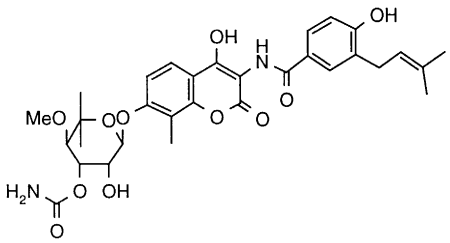
Received 16 November 1999; accepted 12 December 1999

Abstract

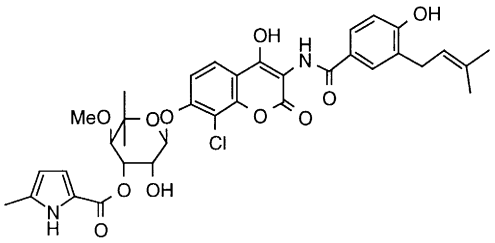
The palladium-catalysed coupling reaction between tosylate derivatives and organostannanes has been investigated as a methodology for carbon–carbon bond formation. Aryl substituents have been successfully incorporated even in highly functionalised coumarin structures to afford new analogues of the antibiotic novobiocin. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: antibacterials; coumarin; sulfonyl compounds; palladium catalyst; organotin reagents.

Novobiocin **1** and clorobiocin **2** are coumarin-derived antibiotics which act as competitive inhibitors of the bacterial ATP binding gyrase B subunit, blocking negative supercoiling of relaxed DNA.[1] These naturally produced antibacterials are extremely active against Gram-positive bacteria especially methicilin-resistant staphylococcus strains.[2] However, their poor pharmacokinetic properties as well as toxicity issues[3] have prevented them from pharmaceutical applications as antibiotics. Consequently, we have embarked on an extensive programme of chemical modifications[4] aiming to improve the pharmacological and pharmacokinetic properties of this class of compounds.



1 novobiocin



2 clorobiocin

We report here an efficient methodology for the preparation of 4-arylcoumarin analogues **4**. The key step relies on an unexpected palladium-catalysed coupling reaction between *p*-toluenesulfonate derivatives **3** and aryltrialkylstannanes **5**.[5]

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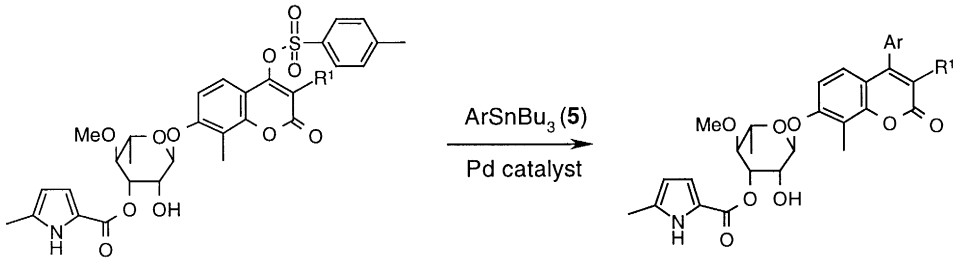
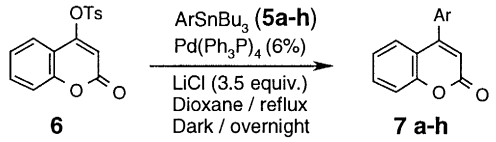
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02351-5



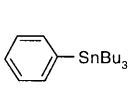
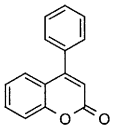
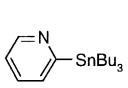
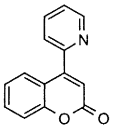
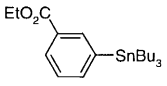
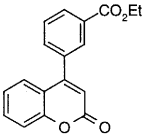
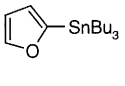
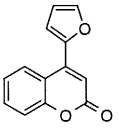
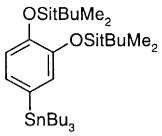
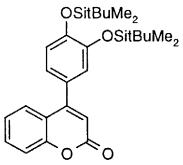
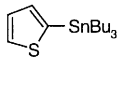
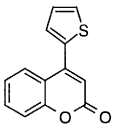
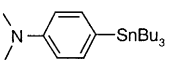
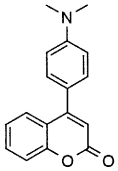
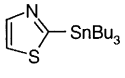
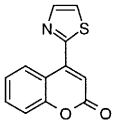
3a,b a:R^1=H; b:R^1=CO_2R **4a,b**

The leaving entity of choice in transition metal-catalysed coupling reactions with organometallic reagents is often the triflate group.[6] However, we could not find a satisfactory methodology for preparing the corresponding trifluoromethanesulfonate analogue of **3b** (R^1=CO_2Bn) because of stability issues. We, therefore, turned our attention to a more stable sulfonate group with the idea that the electron withdrawing coumarin moiety could decrease the electronic density of the C–OSO_2 bond allowing palladium insertion. Preliminary coupling reactions were attempted with the coumarin-derived tosylate **6** using standard Stille conditions (see Table 1).[7]



6 **7 a-h**

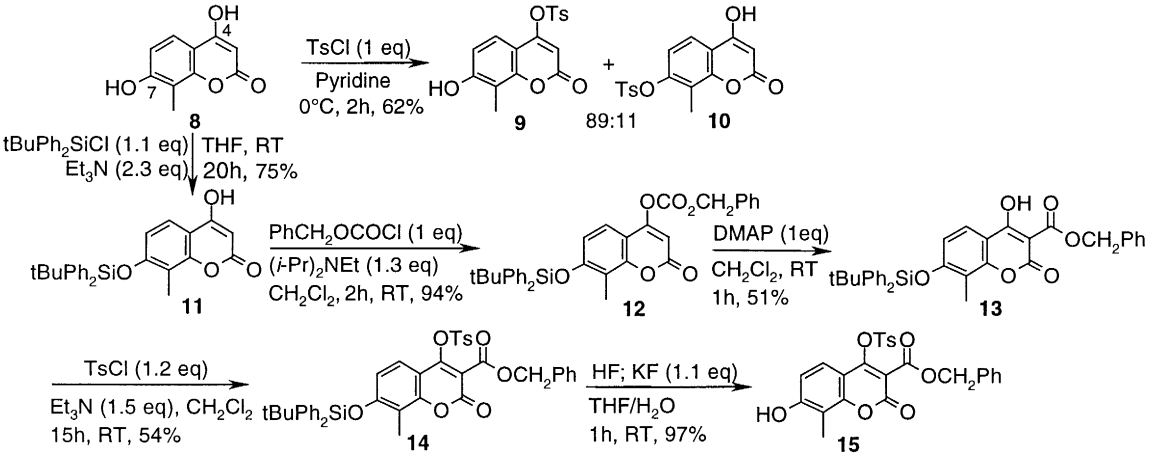
Table 1
Palladium-catalysed coupling reactions between tosylate **6** and various organostannanes **5**

$ArSnBu_3$[b]	Product	Yield (%)[a]	$ArSnBu_3$[b]	Product	Yield (%)[a]
		60			14
5a	**7a**		**5e**	**7e**	
		65			74
5b	**7b**		**5f**	**7f**	
		46			61
5c[c]	**7c**		**5g**	**7g**	
		54			<5
5d[c]	**7d**		**5h**	**7h**	

[a] The yields refer to single runs and are given for pure products isolated by flash chromatography on silica gel.
[b] 1.25 equiv. organostannane was added.
[c] Prepared from the corresponding arylbromide derivative by exchange reaction (*s*-BuLi) followed by transmetallation reaction (Bu_3SnCl).

We were delighted to observe that organostannane **5a** underwent the coupling reaction with an acceptable yield (60%). Furthermore, the scope of the tosylate-assisted coupling reaction was extended to functionalised aryl reagents (**5b**–**d**). In addition, the reaction took place effectively with heterocycle-derived stannanes (**5f**, **5g**) albeit occurring in low yield from the pyridine derived reactant **5e**. Among the organostannanes investigated, only **5h** failed to give the desired coupled compound (**7h**). No further studies were carried out to optimise these results. The developed methodology was applied promptly to the synthesis of 4-arylcoumarin analogues of novobiocin.

The preparation of the key coumarin intermediates **9** and **15** from dihydroxycoumarin **8** is depicted in Scheme 1.



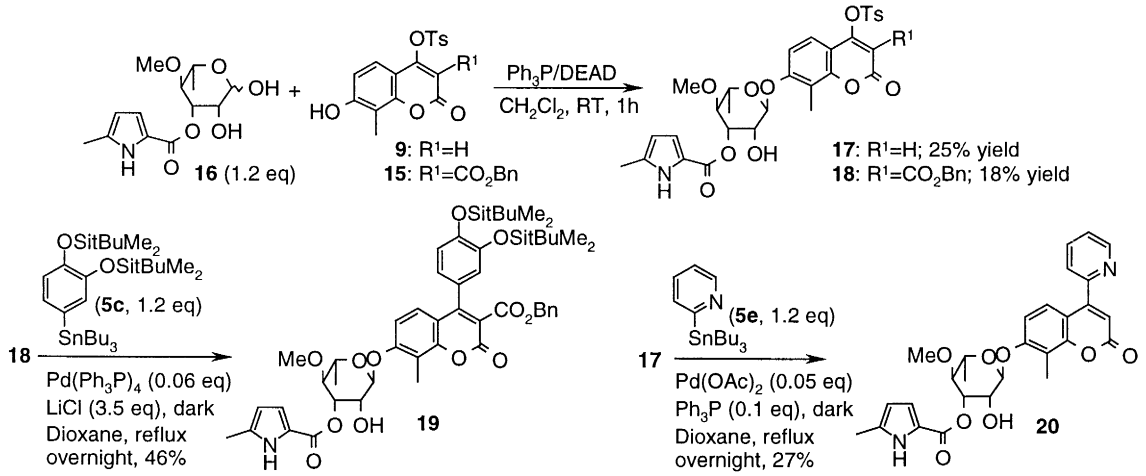
Scheme 1.

It is worthy of note that tosylation of **8** in pyridine occurred predominately at the O-4 position whereas silylation using triethylamine led exclusively to the 7-silyl ether derivative **11**. Introduction of the carboxy group at the C-3 position was realised by Fries-type rearrangement of the 4-acyloxy derivative **12**.[4a,8] Tosylation of **13** was successful in dichloromethane in the presence of triethylamine. The 7-O *t*-butyldiphenylsilyl ether was then cleaved cleanly using HF/KF in a water–THF mixture[9] to afford **15**.

The desired α-glycosides **17** and **18** were obtained by coupling L-rhamnopyranoside **16**[4c] with the coumarins **9** and **15** using Mitsunobu's conditions (see Scheme 2).[10] Tosylate derivatives **17** and **18** were then submitted to cross-coupling with organostannanes **5c** and **5e** in the presence of palladium catalysts.

The catechol moiety was successfully introduced at the coumarin C-4 position from tosylate **18** to afford the corresponding analogue **19** of novobiocin.[11] The yield obtained with $Pd(Ph_3P)_4$ as catalyst was satisfactory considering the high level of functionalisation as well as the unprotected groups in the starting substrate structure **18**. On the other hand, the coupling reaction performed with the pyridine-derived stannane **5e** led to partial degradation of tosylate **17** when catalysed with $Pd(Ph_3P)_4$ or $PdCl_2(Ph_3P)_2$. Finally, the pyridine containing derivative **20** was accessible in conditions generating in situ zero-valence palladium ($Pd(OAc)_2/Ph_3P$).[12]

In conclusion, we have developed a new variation to the methodology for carbon–carbon bond formation by a palladium-catalysed coupling reaction. In this respect, we have shown that the *p*-toluenesulfonyl group constitutes an efficient alternative to the widely used trifluoromethanesulfonyl moiety as a leaving group. Ease of preparation as well as chemical stability contribute to the attractiveness of the tosylate group over triflate. The developed methodology has been applied to the convergent synthesis of 4-arylcoumarin analogues of novobiocin in the search for new antibacterial clinical candidates.



Scheme 2.

Acknowledgements

We are grateful to Didier Babin (Medicinal Chemistry) for assistance and to Didier Ferroud (Chemical Development) for fruitful discussions.

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11. From **17**, the coupling reaction with **5c** realised in the same experimental conditions occurred in 34% yield.
12. Preparation of **20**: a mixture of tosylate **17** (129 mg, 0.21 mmol), organostannane **5e** (93 mg, 0.25 mmol), $Pd(OAc)_2$ (9.7 mg, 0.019 mmol) and Ph_3P (10.4 mg, 0.039 mmol) was stirred overnight in refluxing dioxane (5 ml). After concentration at

reduced pressure the reaction mixture was purified by flash chromatography on silica gel (hexane:ethyl acetate: 30:70 v/v) to afford **20** (30 mg, 27% yield). TLC, SiO_2, hexane:ethyl acetate: 30:70 (v/v), R_f=0.27; IR ($CHCl_3$, ν cm^{-1}): 3608 (OH), 3448 (C═C-NH), 1714, 1696 (C═O), 1603, 1567, 1491 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 9.07 (m, NH), 8.78 (m, 1H), 7.88 (t, J=8 Hz, 1H), 7.6–7.4 (m, 3H), 7.06 (d, J=9 Hz, 1H), 6.76 (m, 1H), 6.18 (s, 1H), 5. 92 (m, 1H), 5.44 (s, 1H), 5.37 (dd, J=10 Hz, J=3 Hz, 1H), 3.94 (m, 1H), 3.70 (m, 1H), 3.49 (s, 3H), 3.46 (t, J=9 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.26 (d, J=6 Hz, 3H). MS *m/e* (relative intensity): 521 (MH^+, 15), 268 (53), 254 (35), 108 (100).