Pergamon

Tetrahedron Letters 39 (1998) 5281–5284

TETRAHEDRON LETTERS

Palladium-catalysed Substitution Reactions of *geminal* Allylic Diacetates

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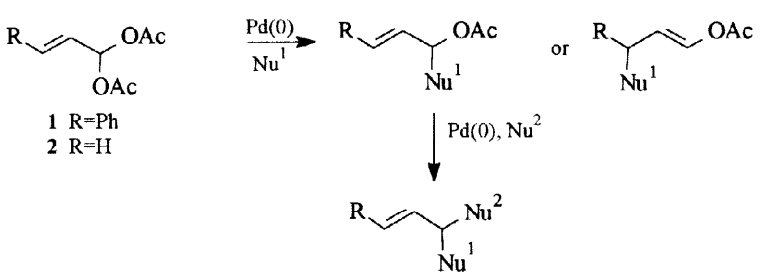
Received 2 April 1998; accepted 12 May 1998

Abstract

The Pd(0)-catalysed substitution of allylic 1,1-diacetates by both carbon and oxygen nucleophiles is described. The products isolated resulted from either single or double substitution reactions.

Keywords: Palladium and compounds; allylation; substitution

Although *geminal* allylic diacetates are readily available from the corresponding α,β-unsaturated aldehydes [1,2], these compounds have received little attention as substrates for palladium(0)-catalysed substitution reactions. The presence of two allylic leaving groups in these compounds theoretically permits the introduction of two different nucleophiles in two stepwise palladium-catalysed substitution reactions (Scheme 1). Huang and Lu [3] were the first to investigate this reaction, and they found that stabilised carbon nucleophiles attacked the acetate carbonyl which lead to the formation of the aldehyde and unwanted substitution products. In contrast to these results, several groups [4-8] obtained monosubstituted



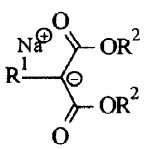
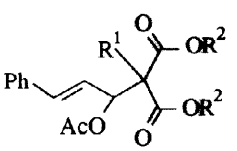
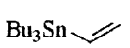
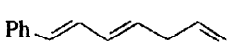
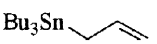
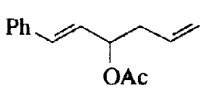
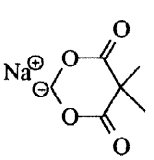
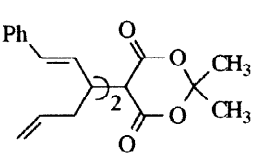
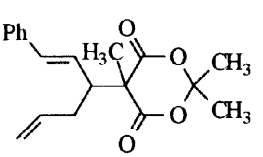
Scheme 1

PII: S0040-4039(98)01000-4

products, and only in the case of a bidentate nucleophile, where the second substitution reaction occurred intramolecularly, was disubstitution observed [4]. The introduction of two different nucleophiles to the title substrates was hitherto not realised.

In this Letter we report our results on studies directed towards the disubstitution of *gem*-allylic diacetates with two different types of nucleophiles. It has been established previously [4] that reaction of allylic diacetates with diethyl malonate in the presence of a base yielded a diene (as a result of acetic acid elimination from the monosubstituted product). We were, therefore, confined to the use of tertiary nucleophiles. With **3** as nucleophile, only the monosubstituted product **4** was obtained, and subsequent treatment of **4** with sterically less hindered stabilised carbon nucleophiles, *e.g.* the sodium salt of diethyl malonate, did not yield any products. Analogous products were obtained with the sodium salts of diethyl nitromalonate (**5**) and diethyl acetamidomalonate (**7**), respectively, as nucleophiles (Table 1, entries 2 and 3). Since

Table 1
Palladium-catalysed substitution reactions with cinnamyl diacetate (1) as substrate.

ENTRY	SUBSTRATE	NUCLEOPHILE	PRODUCT	YIELD[a]
				
1	1	3 R^1=CH_3, R^2+R^2=$C(CH_3)$	4 R^1=CH_3, R^2+R^2=$C(CH_3)_3$	80%
2	1	5 R^1=NO_2, R^2=CH_2CH	6 R^1=NO_2, R^2=CH_2CH_3	25%
3	1	7 R^1=NHAc, R^2=CH_2CH_3	8 R^1=NHAc, R^2=CH_2CH_3	56%
4	1	 9	 10	90%[b]
5	1	 11	 12	83%[c]
6	12	 13	 14	50%[d]
7	12	3	 15	40%[e]

[a] Unless otherwise stated, the following reaction conditions were used: 0.1 eq. $Pd(PPh_3)_4$, THF, RT, 6 h; [b] 0.3 Eq. $Pd(dba)_2$, 3 eq. LiCl, DMF, RT, 3 h; [c] RT, 16 h; [d] Reflux, 2 h; [e] Reflux, 12 h

the failure of the second nucleophile to react with **4**, **6** and **8** can most likely be attributed to steric hindrance, we focused our attention on sterically less demanding nucleophiles.

Reaction of **1** with tributylvinyltin (**9**) as the nucleophile (Table 1, entry 4) resulted in the formation of the disubstituted product **10**. The product is formed by attack of the second nucleophile on the terminal position of the π-allyl palladium complex obtained from the monosubstituted product. In contrast, the reaction of **1** with one equivalent of allyltributyltin (**11**) in the presence of $Pd(PPh_3)_4$ resulted in the formation of the monosubstituted product **12** in 83% yield. This reaction reflected the lower reactivity of the internal allylic acetate as compared to the terminal allylic acetate (obtained from the vinyltin derivative), where only the disubstituted product **10** could be isolated, even in the presence of only one equivalent of nucleophile.

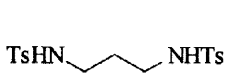
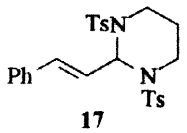
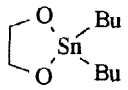
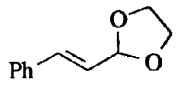
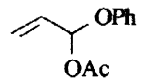
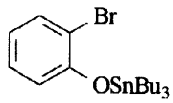
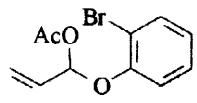
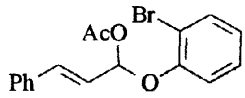
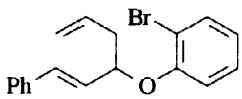
With the monosubstituted product **12** in hand, we attempted reaction with a second, more bulky nucleophile. The palladium-catalysed reaction of **12** with the anion of Meldrum's acid (**13**) allowed the introduction of the second nucleophile. However, the acidity of the α-proton in the product resulted in the formation of doubly substituted Meldrum's acid **14** (Table 1, entry 6). With nucleophile **3** only the expected product **15** was formed. We found that the order of the two reactions could be reversed, and that treatment of **4** with allyltributyltin in the presence of $Pd(PPh_3)_4$ also resulted in the formation of **14**, albeit in much lower yield (20%). Treatment of the sterically more hindered **6** with **11** did not result in formation of any of the required products.

Reactions involving heteroatom nucleophiles were also investigated (Table 2). The palladium-catalysed reaction of **1** proceeds with both the tosylated derivative of 1,3-diaminopropane (**16**) and the stannylene derivative of ethylene glycol to yield the disubstituted products (Table 2, entries 1 and 2). We have utilised the latter reaction in carbohydrate chemistry to provide a selective protecting group for two vicinal hydroxyl groups [8].

Reaction of allylic diacetates with an excess of the tributyltin derivative of phenol led mainly to the bisphenoxy substituted product. However, under carefully controlled experimental conditions, we could prepare the monosubstituted phenoxy derivative **21** (Table 2, entry 3). Starting from 2-bromophenol, the analogous products **23** and **24** could be prepared (entries 4 and 5). This reaction was also successfully performed with the allyl derivative **12** (Table 1, entry 5) as substrate, resulting in the formation of **22** (Table 2, entry 6). Although the yields of these reactions are modest at this stage, these compounds contain interesting combinations of functionalitity and they certainly have potential as synthetic precursors.

This work has proved that disubstitution of geminal allylic acetates is possible not only in an intramolecularly fashion with bidentate nucleophiles, but also in intermolecular fashion with both carbon and oxygen nucleophiles. The prerequisite for an intermolecular substitution with two different type of nucleophiles is that, due to steric hindrance, only one bulky stabilised carbon nucleophile can be used.

Table 2
Palladium-substitution reactions with heteroatom nucleophiles

ENTRY	SUBSTRATE	NUCLEOPHILE	PRODUCT	YIELD[a]
1	1			16%[b]
		16	17	
2	1			34%[c]
		18	19	
3	2	$PhOSnBu_3$		26%[d]
		20	21	
4	2			14%[c]
		22	23	
5	1	22		30%[f]
			24	
6	12	22		12%[g]

[a] Reactions were conducted in THF with 0.1 eq. of $Pd(PPh_3)_4$; [b] Reflux, 5 h; [c] RT, 16 h, product not very stable; [d] Reflux, 6 h; [e] 0.2 Eq. DPPP, reflux, 24 h; [f] 0.2 Eq. DPPP, reflux, 24 h [g] 0.2 Eq. DPPP, RT, 18 h.

Acknowledgements

The financial support by the Foundation for Research Development and SASOL is gratefully acknowledged.

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