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Reactivity of Quinoline- and Isoquinoline-Based Heteroaromatic Substrates in Palladium(0)-Catalyzed Benzylic Nucleophilic Substitution

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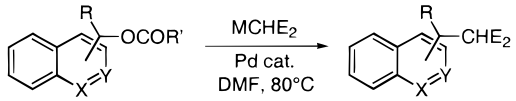
ABSTRACT

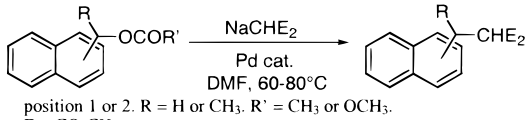


X,Y = N, CH or CH, N. R = H or CH_3. M = Na, K or Cs. E = CO_2CH_3.

Quinolylmethyl, 1-(isoquinolyl)ethyl, and 1-(quinolyl)ethyl acetates reacted with dimethylmalonate anion in the presence of a Pd(0) catalyst to give products of nucleophilic substitution and/or byproducts, depending upon the substitution pattern. The observed side reactions were reduction in the case of primary acetates and elimination or elimination/Michael-type addition sequence for secondary substrates.

We described in recent years the formation of a benzylic carbon−carbon bond by the palladium(0)-catalyzed nucleophilic substitution of naphthylmethyl and 1-(1- or 2-naphthyl)ethyl acetates and carbonates by sodium dimethyl malonate (Scheme 1).[1] This method has been extended to the formation of a carbon−nitrogen bond by using amines as nucleophiles.[2]

Scheme 1



position 1 or 2. R = H or CH_3. R' = CH_3 or OCH_3. E = CO_2CH_3.

We report in this communication the substitution of *N*-heteroaromatic substrates **1**−**3** (Figure 1) derived from quinoline and isoquinoline. We recently described the reactivity of 4-quinolylmethyl acetate **1c** and other 4-quinolylmethyl esters in the palladium-catalyzed substitution by formate anion (formation of a carbon−hydrogen bond).[3]

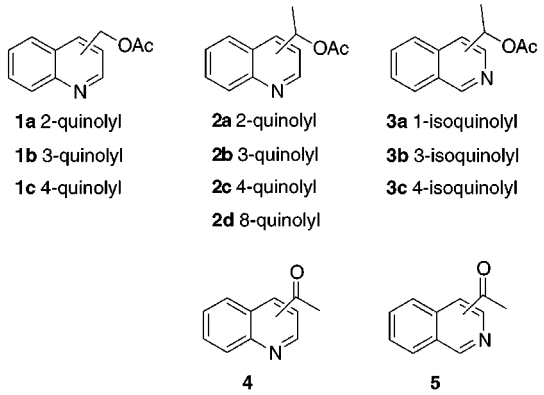


Figure 1. Structure of compounds **1**−**5**.

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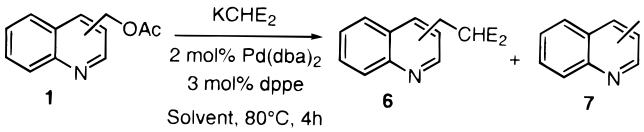
Acetates **1** were prepared by reduction/acetylation of the commercialy available quinolinecarboxaldehydes. Acetates **2** and **3** were obtained similarly from the corresponding arylmethyl ketones **4** and **5**. We recently developed a new preparation of compounds **4** and **5** from quinolyl and isoquinolyl derivatives (chlorides, bromides, or triflates) via palladium-catalyzed Stille and Heck coupling reactions.[4] The secondary acetates **2**[5] and **3**[6] were also prepared in lower yields by literature methods.

We first studied the reactivity of primary acetates **1** (Table 1). The nucleophile was preformed by mixing dimethylmalonate and potassium *tert*-butoxide. Substrate **1a** was totally unreactive under the conditions described below (entry 1). At higher (100 °C) temperature, a slow degradation was observed but the expected substitution product **6a** was never obtained.

Table 1. Substitution of Primary Acetates **1**[a]



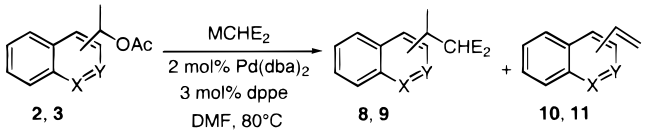
entry	substrate	solvent	product **6** (%)	product **7** (%)
1	**1a**	DMF		
2	**1b**	DMF	**6b** (23)	**7b** (74)
3	**1c**	DMF	**6c** (55)	**7c** (24)
4[b]	**1c**	DMF	**6c** (49)	**7c** (21)
5	**1b**	THF	**6b** (80)	
6	**1c**	THF	**6c** (66)	

[a] Isolated yields. [b] $NaCH(CO_2CH_3)_2$ (from NaH and dimethylmalonate) as nucleophile.

In contrast, acetates **1b** and **1c** displayed good reactivity with total consumption of the substrate in less than 4 h. The 1- and 2-naphthylmethyl acetates achieved 100% conversion in more than 5 h. However, in addition to the expected substitution products **6b** and **6c**,[7] 3- and 4-methylquinolines **7b** and **7c**, resulting from a formal reduction process, were obtained (entries 2 and 3). Sodium dimethylmalonate gave essentially the same result (entry 4), but the solvent was the source of this side reaction. Switching from DMF to THF allowed for a selective and high-yielding substitution reaction (entries 5 and 6).[8] It is worth noting that under the same reaction conditions reduction products (i.e., 1- and 2-methylnaphthalenes) were never detected from naphthylmethyl acetates.[1a]

The substitution of secondary acetates **2** and **3** were next examined (Table 2). These substrates did not give reduction products, ethylquinolines and ethylisoquinolines, respectively. In addition to the expected substitution products **8** and **9** a competitive elimination pathway leading to vinylquinolines **10** and vinylisoquinolines **11** was observed. This side reaction was also previously observed in the substitution of 1-naphthylethyl acetates.[1b,c]

Table 2. Substitution of Secondary Acetates **2** and **3**[a]



entry	substrate	M	*t* (h)	substitution product (%)	elimination product (%)
1	**2b**	Na	10	**8b** (61)	**10b** (3)
2	**2b**	K	8	**8b** (59)	**10b** (7)[b]
3	**2b**	Cs	8	**8b** (54)	**10b** (7)
4	**2c**	Na	24	**8c** (74)	**10c** (<5)[b]
5[c]	**2d**	Na	24	**8d** (14)	**10d** (29)
6[d]	**3b**	Na	24	**9b** (13)[b]	**11b** (21)[b]
7	**3c**	Na	24	**9c** (78)	**11c** (11)
8	**3c**	K	24	**9c** (44)	**11c** (12)
9	**3c**	Cs	24	**9c** (60)	**11c** (20)

[a] Isolated yields. [b] Proportion of product from ^{1}H NMR spectrum. [c] 52% isolated **2d** recovered. [d] 66% (from ^{1}H NMR) **3b** recovered.

The extent of elimination was dependent upon the counterion of the nucleophile. This effect was studied in the case of the two substrates **2b** and **3c** (entries 1−3 and 7−9). These compounds were the most reactive, being consumed in 8−10 h for the former and 24 h for the latter. The cesium salt (from dimethylmalonate and cesium carbonate) gave the larger amount of **10b** (13%) and **11c** (33%). In contrast, use of sodium dimethylmalonate (from sodium hydride and dimethylmalonate) minimized the elimination process and led to better isolated yields of **8b** (61%) and **9c** (78%).

Under these optimized conditions, 1-(4-quinolyl)ethyl acetate **2c** reacted cleanly to give **8c** in 74% isolated yield with less than 5% 4-vinylquinoline **10c** detected by ^{1}H NMR analysis of the crude reaction mixture (entry 4).

The other acetates were less reactive compounds; **2d** and **3b** only gave a partial conversion after 24 h, leading predominantly to the elimination products **10d** and **11b**,

(1) (a) Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1992**, *33*, 2509−2510. (b) Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron* **1995**, *51*, 3235−3246. (c) Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899−1902.

(2) Toffano, M.; Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1997**, *38*, 77−80.

(3) (a) Boutros, A.; Legros, J. Y., Fiaud, J. C. *Tetrahedron Lett.* **1999**, *40*, 7329−7332. (b) Boutros, A.; Legros, J. Y., Fiaud, J. C. *Tetrahedron*, accepted for publication.

(4) Legros, J. Y., Primault, G., Fiaud, J. C., unpublished work.

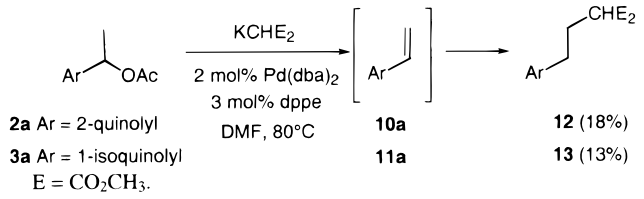
(5) Taylor, R. *J. Chem. Soc. B* **1971**, 2382−2387.

(6) Glyde, E., Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1783−1791.

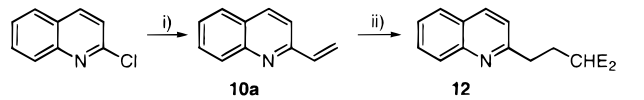
(7) All new compounds were characterized by proton and carbon-13 NMR, IR, and either HRMS or elemental analysis.

(8) To investigate the nature of the reducing agent, we performed the same reaction as above on acetate **1b** in DMF-d_7; no reduction product was detected in these conditions.

Scheme 2



Scheme 3



i) $H_2C{=}CHSnBu_3$, 4 mol% $Pd(dba)_2$, 8 mol% PPh_3, toluene reflux, 24h (48%). ii) $NaCHE_2$, DMF, 80°C, 48h (67%).
E = CO_2CH_3.

respectively (entries 5 and 6). Attempts to improve the reactivity were unsuccessful; at 100 °C, 8-vinylquinoline **10d** was obtained in 83% yield (calculated by ^{1}H NMR) from **2d**.

Substrates **2a** and **3a** showed a different behavior. Instead of substitution (**8a** and **9a**) and/or elimination (**10a** and **11a**) products, the linear isomers of the former products (**12** and **13**) were produced in low yields, the major products being the unreacted acetates (Scheme 2). The formation of **12** and **13** could be explained by a Michael-type addition of the nucleophile on electron-deficient vinylarenes **10a** and **11a** that result from the elimination process. This reactivity was already reported in the literature.[9]

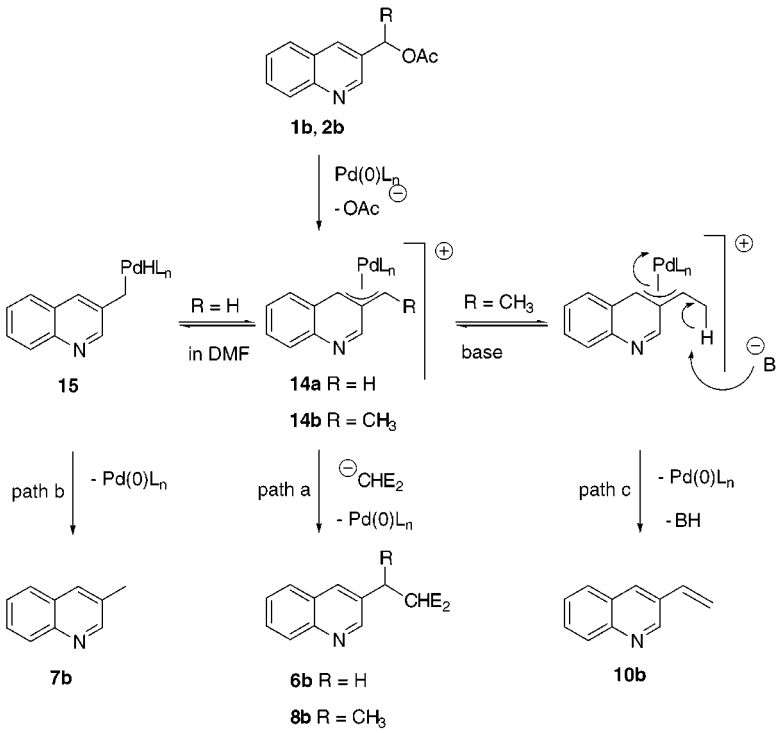
To verify this hypothesis, compound **10a** was prepared from commercially available 2-chloroquinoline by a Stille coupling reaction with tri(*n*-butyl)vinylstannane (Scheme 3).[10] Subjecting **10a** to the substitution reaction conditions in the presence or absence of the palladium catalyst produced compound **12** in both cases at approximately the same rate; evidently the palladium is not involved in this readdition process.

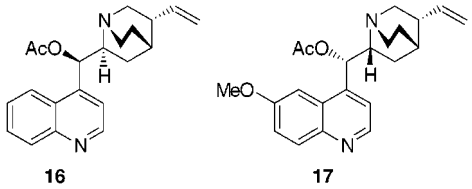
These results can be rationalized according to Scheme 4, which illustrates the different pathways in the case of acetates **1b** and **2b**. After oxidative addition of the substrate on a palladium(0) complex,[1−3] a nucleophilic attack of the dimethylmalonate anion on the cationic η^3-benzylpalladium intermediate **14** leads to the substitution product **6b** or **8b** (path a). From **14a** (R = H) in DMF only, a hydride source gives the neutral hydrido complex **15** and finally reduction product **7b** after reductive elimination (path b). The nature of this hydride source is presently unknown, but the DMF is involved in its formation. In the case of **14b** (R = CH_3), an E2-type base-promoted elimination gives **10b** (path c).[11]

Finally, the acetates of cinchonidine **16** and of quinidine **17** (Figure 2) were prepared to extend this reaction to natural product derivatives. However, the corresponding substitution (or elimination) products were not detected after 7 days, at 80 °C in DMF or even at 140 °C in DMA. This inertness may result from steric hindrance and/or the presence of the basic nitrogen of the quinuclidine moiety.

In conclusion, the palladium-catalyzed nucleophilic substitution of heteroaromatic benzylic acetates was investigated.

Scheme 4





16 17

Figure 2. Acetates of cinchonine and quinidine.

The relative positions of the nitrogen and of the acetoxymethyl or acetoxyethyl substituent are crucial for the course of the reaction. In the case of 2-substituted quinoline and 1- or 3-substituted isoquinoline substrates, no (in the case of **1a**, **2a**, and **3a**) or little (for **3b**) substitution occurs. The 3- and 4-substituted quinoline and the 4-substituted isoquinoline substrates exhibit a higher reactivity than their analogues derived from naphthalene. Concerning 1-(8-quinolyl)ethyl acetate **2d**, the lack of reactivity observed can probably be attributed to the proximity of the neighboring nitrogen atom.[12]

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(9) (a) Oda, R.; Teramura, K.; Tanimoto, S.; Nomura, M.; Suda, H.; Matsuda, K. *Bull. Inst. Chem. Res. Kyoto Univ.* **1955**, *33*, 117−125. (b) Boekelheide, V.; Sieg, A. L. *J. Org. Chem.* **1954**, *19*, 587−592.

(10) Compound **10a** was already prepared by a Stille reaction on 2-quinolyl triflate: Crisp, G. T.; Papadopoulos, S. *Aust. J. Chem.* **1989**, *42*, 279−285.

(11) An alternative mechanism for the formation of **10b** is to consider a β-elimination from an η^1-palladium intermediate analogous to **14b**; because of the electron-withdrawing properties of the pyridinic nitrogen atom, the aromatic C=C double bond is very likely to be weakly interacting with palladium. We thank one of the referees for this suggestion.

(12) **Representative Experimental Procedure** (Table 2, entry 4). 1-(4-Quinolyl)ethyl acetate **2c** (215 mg, 1 mmol) in 1 mL of DMF was added under argon to a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and dppe (12 mg, 0.03 mmol) in 1 mL of DMF. After 0.25 h of stirring, this solution was added to a suspension of sodium dimethylmalonate [from NaH (48 mg, 2 mmol) and $CH_2(CO_2CH_3)_2$ (0.23 mL, 2 mmol)]. The reaction mixture was stirred at 80 °C for 24 h and then diluted with ether (20 mL), and the organic phase washed with 2 × 10 mL of a solution of saturated $NaHCO_3$. The aqueous phases were extracted with ether (3 × 10 mL), and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 70:30) to give dimethyl 2-(1-(4-quinolyl)ethyl)propanedioate **8c** (212 mg, 0.74 mmol, 74%).