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A novel arylation of arylacetic acid esters using tertiary arylamines and $TiCl_4$

Mariappan Periasamy,* N. KishoreBabu and Keela Natarajan Jayakumar

School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India

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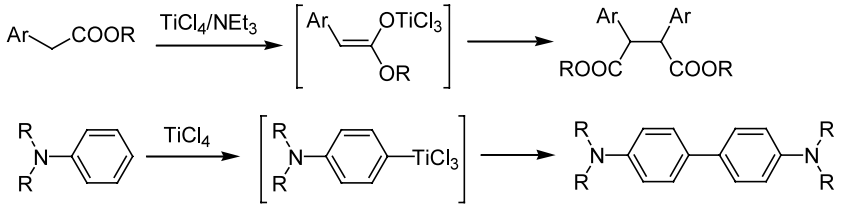
Abstract—The reactions of arylacetic acid esters with tertiary arylamines in the presence of $TiCl_4$ give α-arylated products in 65–90% yields, as well as 10–20% yields of the corresponding benzidines.

In recent years, the $TiCl_4/R_3N$ reagent system has been extensively used in organic synthesis.[1] This reagent system is useful for the oxidative coupling of arylacetic acid esters (Scheme 1).[2] *N*,*N*-Dialkylanilines also undergo oxidative coupling in the presence of $TiCl_4$ to give the corresponding benzidine derivatives (Scheme 1).[3]

We report that arylacetic acid esters react with tertiary arylamines to give the corresponding cross coupled products. We observed that the reaction of the aryltitanium species with methyl phenylacetate produced the corresponding α-arylated products in good yields (Scheme 2). For example, the reaction of *N*,*N*-dimethylaniline and methyl phenylacetate with $TiCl_4$ at 0–25°C for 5 h produced **1a** in 89% yield, as well as the corresponding benzidine derivative (10%).[4] The diarylacetic esters were readily separated from the benzidines by a usual workup.

The reaction was found to be general and several other tertiary arylamines and arylacetic acid esters were found to give the corresponding cross-coupled products under these conditions (see Scheme 2). The results are summarized in Table 1. The formation of the cross-coupled products may be explained by considering cross-coupling between the titanium enolate of the esters and the aryltitanium species formed in situ (Scheme 3). Initially, the reaction of *N*,*N*-dialkylarylamines with $TiCl_4$ would produce aryltitanium intermediates.[3] The $TiCl_4$–ester complex could be deprotonated by the *N*,*N*-dialkylarylamine present which would lead to the formation of titanium enolates that on cross-coupling with the aryltitanium species produce the corresponding diarylacetic esters.

In this reaction, the arylating agent *N*,*N*-dialkylarylamine also acts as a base in the titanium enolate formation (Scheme 3). We observed that enolizable



Scheme 1.

Keywords: diaryl acetic esters; cross coupling reactions; titanium enolates; aryltitanium.
* Corresponding author.

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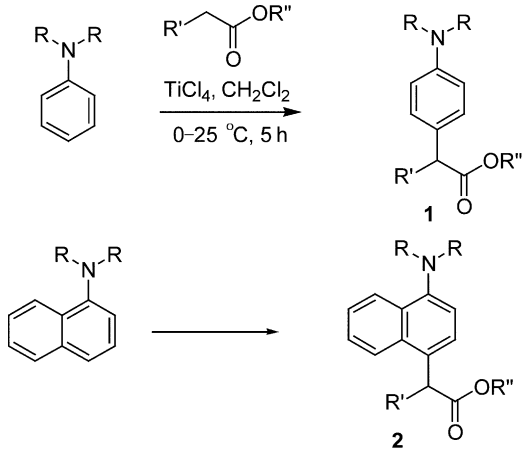


Scheme 2.

Table 1. Reaction of arylacetic acid esters with arylamines and $TiCl_4$

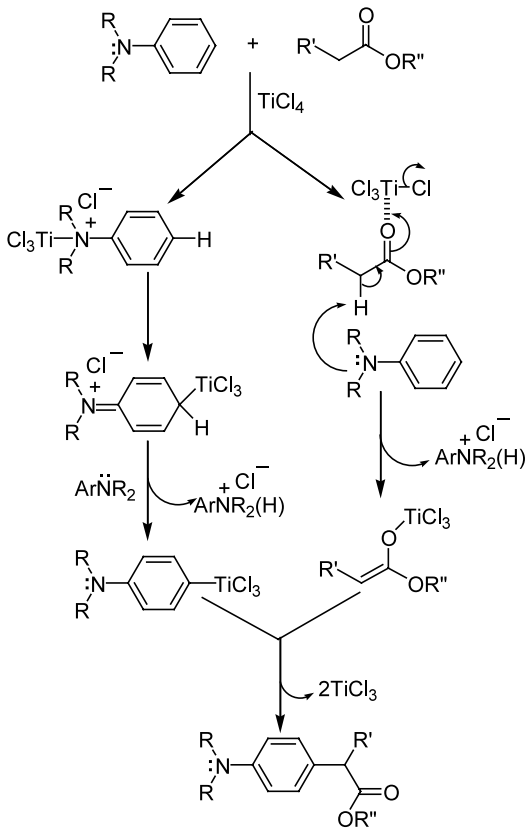
S. No	$ArNR_2$	Ester	Product[a]	Yield[b] (%)
1	Ar = Ph, R = CH_3	R′ = Ph, R″ = C_2H_5	**1a**	89
2	Ar = Ph, R = C_2H_5	R′ = Ph, R″ = C_2H_5	**1b**	90
3	Ar = Ph, R = CH_3	R′ = 1-Np, R″ = CH_3	**1c**	88
4	Ar = Ph, R = C_2H_5	R′ = 1-Np, R″ = CH_3	**1d**	76
5	Ar = Ph, R = CH_3	R′ = Ph, R″ = CH_3	**1e**	86
6	Ar = Ph, R = C_2H_5	R′ = Ph, R″ = CH_3	**1f**	81
7	Ar = 1-Np R = CH_3	R′ = Ph, R″ = C_2H_5	**2a**	76
8	Ar = 1-Np, R = CH_3	R′ = Ph, R″ = CH_3	**2b**	65
9	Ar = 1-Np, R = CH_3	R′ = 1-Np, R″ = CH_3	**2c**	68

[a] The products were identified by ^1H, ^{13}C NMR and mass spectral data[5] and by comparison with the data reported for compound **1a**.[6]

[b] In all reactions, $TiCl_4$ (10 mmol), arylamine (7.5 mmol) and the arylacetic acid ester (2.5 mmol) were used. Yields of products isolated by column chromatography are based on the amount of ester used. In all cases, the corresponding benzidine (up to 20%) as well as small amounts of unidentified mixtures of polar products were also isolated.

esters like methyl propionate did not react with the aryltitanium species under these reaction conditions, possibly due to the weaker basicity of the arylamines for the formation of enolates.

The synthesis of this new class of α-aryl esters is of interest because certain diarylacetic acid derivatives are known to be biologically active.[7] This new method of α-arylation is relatively simple compared to other methods of α-arylation for esters[6] and hence will help in the synthesis of this important class of organic compounds.



Scheme 3.

Acknowledgements

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4. *Representative procedure for the reaction of N,N-dimethylaniline and ethyl phenylacetate with $TiCl_4$*: In CH_2Cl_2 (25 mL), *N*,*N*-dimethylaniline (0.9 mL, 7.5 mmol) and ethyl phenylacetate (0.35 ml, 2.1 mmol) were dissolved at 0°C

under N_2. $TiCl_4$ (2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. The reaction mixture was stirred at 0°C for 0.5 h and at 0–25°C for 5 h. Saturated aqueous K_2CO_3 (10 mL) was added and the mixture stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted amine was eluted using 1:99 EtOAc/hexane mixture. The *N*,*N*,*N*′,*N*′-tetramethylbenzidine (0.089 g, 10%) and aminoester **1a** (0.528 g, 89%) were eluted next.

5. **Representative spectral data**: ^{13}C NMR (50 MHz, $CDCl_3$) spectral data for compounds **1a**–**2c**. **1a**: ^{13}C NMR (δ ppm) 173.0, 149.8, 139.7, 129.3, 128.5, 128.5, 126.9, 126.8, 112.7, 60.9, 56.4, 40.6, 14.2. **1b**: ^{13}C NMR (δ ppm) 173.1, 147.0, 139.8, 129.5, 128.5, 128.4, 126.9, 125.5, 111.9, 60.9, 56.3, 44.4, 14.2, 12.6. **1c**: ^{13}C NMR (δ ppm) 173.9, 150.0, 135.5, 134.2, 131.9, 129.8, 129.1, 128.1, 126.6, 126.3, 125.7, 125.6, 123.5, 112.8, 53.0, 52.4, 40.6. **1d**: ^{13}C NMR (δ ppm) 174.0, 147.2, 135.5, 134.1, 129.9, 129.0, 127.9, 126.5, 126.3, 125.6, 125.5, 124.4, 123.4, 112.0, 52.8, 52.3, 44.4, 12.7. **1e**: ^{13}C NMR (δ ppm) 173.6, 149.9, 139.6, 129.4, 128.6, 127.4, 127.1, 126.5, 112.7, 56.3, 52.2, 40.6. **1f**: ^{13}C NMR (δ ppm) 173.5, 147.1, 139.6, 129.5, 128.5, 128.5, 127.0, 125.2, 111.8, 56.2, 52.1, 44.3, 12.6. **2a**: ^{13}C NMR (δ ppm) 173.0, 150.7, 138.4, 132.9, 129.3, 129.0, 128.6, 127.2, 126.3, 126.2, 125.0, 124.9, 123.6, 113.5, 61.2, 53.5, 45.2, 14.2. **2b**: ^{13}C NMR (δ ppm) 173.5, 150.8, 138.3, 132.9, 129.3, 129.0, 128.6, 127.3, 126.3, 125.1, 124.9, 123.6, 113.5, 53.4, 52.4, 45.2. **2c**: ^{13}C NMR (δ ppm) 173.8, 150.8, 134.4, 134.1, 132.9, 131.8, 129.4, 129.0, 128.2, 127.7, 126.7, 125.7, 125.6, 125.2, 123.4, 123.1, 113.7, 52.5, 50.1, 45.3.
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