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$TiCl_4$-mediated amination of propargylic esters

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Abstract—The $TiCl_4$-mediated substitution of propargylic esters with amides afforded the corresponding α-substituted propargylic amides.

Propargylic amines, which possess strong inhibitory activities toward several enzymes (i.e. monoamine oxidase B,[1] aldehyde dehydrogenase[2]) are ideal starting materials in the synthesis of allylamines, also having highly potent biological activities.[3] Only a few publications dealing with equimolar or multistep procedures for preparing enantiopure α-substituted propargylic amines have been reported.[4] The shortest and most promising route seems to be the direct Lewis acid-mediated nucleophilic displacement reaction of the corresponding propargylic esters.[5,6] This reaction has advantages over previous described methods (amination of propargylic triflates,[7] propargylic halides[8] and allenyl halides[9]) with regard to chemoselectivity, reaction conditions and availability of the starting products. A copper(I)-catalyzed nucleophilic substitution of propargylic esters has already been reported, this reaction is limited to the use of terminal alkynes only.[10] Herein we describe preliminary results of $TiCl_4$-mediated nucleophilic displacement of propargylic esters with amines—our direct approach to unsubstituted propargylic amines.

According to our procedures previously developed for the $TiCl_4$-mediated nucleophilic substitution of propargylic esters with alcohols, we have tried to react primary and secondary amines with propargylic esters under the described conditions. No reactions were observed in any experiments carried out with the 1,3-diphenyl-α-substituted propargylic esters **1a** and **1b** as starting materials. Only the use of 'activated' amines (*p*-toluenesulfonamide and acetamide) provided us with the desired 1,3-diphenyl-α-substituted propargylic amides **2a**–**2e** (Scheme 1, entries 6–10, Table 1). However, by using benzamide in these reactions, more satisfactory results were obtained with regard to reaction time, catalytic execution and yield. Carried out at room temperature, 10 mol% of $TiCl_4$ was sufficient enough for obtaining the propargylic benzamides **2f**–**2i** (entries 11–15, Table 1).[11]

Since α-propargylic amines are unstable compounds,[12] compounds **2f**–**2i** seem to be very useful precursors for the corresponding α-propargylic amines. As an example, the benzoyl group of the amide **2f** was removed by reduction with DIBAL[13] at −78°C to yield 1,3-diphenylprop-2-ynyl-1-amine (**3**) (entry 16, Table 1).[14]

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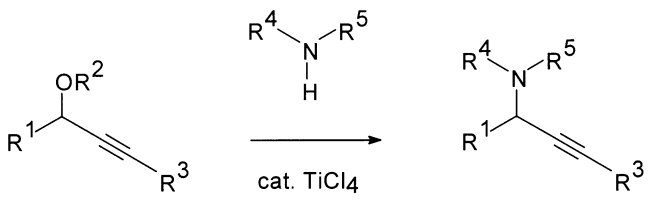

1a - 1e **2a - 2i, 3**

Scheme 1.

Keywords: alkynes; substitution; amides; catalysis.

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Table 1. $TiCl_4$-mediated substitution of propargylic esters with amides

Entry	R^1	R^2	R^3	R^4	R^5	Compound	Yield (%)
1	Ph	*i*Boc	Ph	–	–	**1a**	
2	Ph	Ac	Ph	–	–	**1b**	
3	Ph	Ac	*n*Bu	–	–	**1c**	
4	Ph-≡	Ac	Ph	–	–	**1d**	
5	*n*Bu-≡	Ac	*n*Bu	–	–	**1e**	
6	Ph	–	Ph	Ts	nC_6H_{13}	**2a**	41
7	Ph	–	Ph	Ts	H	**2b**	58
8	Ph	–	Ph	Ts	*n*Pr	**2c**	38
9	Ph	–	Ph	Ts	Allyl	**2d**	21
10	Ph	–	Ph	Ac	H	**2e**	19
11	Ph	–	Ph	Bz	H	**2f**	78
12	Ph	–	Ph	Bz	H	**2f**	43[a]
13	Ph	–	*n*Bu	Bz	H	**2g**	73
14	Ph-≡	–	Ph	Bz	H	**2h**	57
15	*n*Bu-≡	–	*n*Bu	Bz	H	**2i**	51
16	Ph	–	Ph	H	H	**3**	55

[a] **1a** was used as starting material.

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11. All new compounds have been satisfactorily characterized (^1H, ^{13}C NMR, MS, elemental analysis). Preparation of **2f**: A solution of $TiCl_4$ (37.9 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL) was carefully added to a stirred mixture of benzamide (484.6 mg, 4.0 mmol) and (1,3-diphenyl-prop-2-ynyl)-acetate **1b**[15] (500.6 mg, 2.0 mmol). The reaction mixture was stirred for 4–5 h at rt and after completion (TLC control) extracted several times with diethyl ether and aq. $NaHCO_3$. The organic layers were separated, concentrated in vacuo and purified by column chromatography. Compound **2f** (486.0 mg, 78.0%) was isolated. Mp: 167–169°C; (CCl_4) ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (1H, d, $J=8.67$ Hz), 6.65 (1H, d, $J=8.66$ Hz), 7.2–7.8 (15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.62, 85.11, 86.94, 122.42, 126.63, 127.15, 127.19, 127.67, 128.22, 128.34, 128.60, 128.63, 128.82, 131.86, 139.01, 166.21. Preparation of **3**: Benzamide **2f** (311.4 mg, 1 mmol) was dissolved in 2 mL of dry toluene and cooled to −78°C. A solution of DIBAL in hexane (2.0 mL, 2.0 mmol) was carefully added. The reaction was controlled by TLC. At the end of the reaction the mixture was quenched at −78°C with saturated aq. NH_4Cl and extracted several times with diethyl ether. The organic layers were separated, concentrated in vacuo and purified by column chromatography. Compound **3** (114.0 mg, 55.0% yield) was isolated as an oil. The ^1H and ^{13}C NMR data of **3** are identical with those given in Ref. 14.
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