Convenient preparative method for synthesis of methyl (*Z*)-3-aryl-2-(carbobenzoxyamino)acrylates by Wittig—Horner reaction with the use of Et_3N as a base

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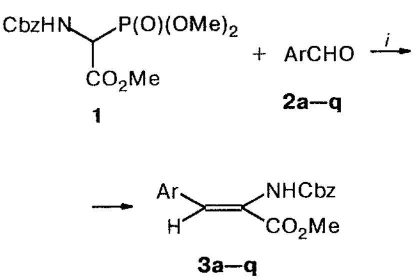
The Wittig—Horner reaction of $CbzNHCH(CO_2Me)P(O)(OMe)_2$ (**1**) with ArCHO (**2**) in the presence of Et_3N as a base affords methyl (*Z*)-3-aryl-2-(carbobenzoxyamino)acrylates (**3**) with high degrees of diastereoselectivity (*Z*)/(*E*) > 10:1. One recrystallization of the crude product is sufficient to obtain isomerically and chemically pure (*Z*)-**3**.

Key words: α,β-dehydro-α-amino acids, Wittig—Horner reaction, diastereoselectivity, triethylamine, (*Z*)-3-aryl-2-(carbobenzoxyamino)acrylates, synthesis.

α,β-Dehydro-α-amino acids (DAA) and their derivatives are representatives of an important class of prochiral substrates, which have been advantageously used for years for enantioselective hydrogenation.[1,2] DAA exist as (*Z*)- and (*E*)-isomers. It has been found that, in some cases, hydrogenation of (*E*)-DAA in the presence of chiral catalysts occurs at a lower rate and with lower enantioselectivity than that of (*Z*)-DAA.[3] Since most of the methods of synthesis of DAA afford mixtures of isomers, the need for facile and efficient preparative-scale procedures for preparing individual isomers of DAA is obvious.

Recently a convenient method for the synthesis of DAA involving the Wittig—Horner olefination of carbonyl compounds with 2-(alkoxyphosphinyl)glycine derivatives (Scheme 1) has been suggested.[4,5] The mild conditions of this reaction make it possible to use Boc- or Cbz-derivatives (*tert*-butoxycarbonyl- and carbobenzoxy-derivatives, respectively); thus, this method becomes promising for the synthesis of precursors of peptides.

Scheme 1



i. Base

A base, under whose action olefination takes place, plays a significant role in this method. Nitrogen-containing bases such as 1,8-diazabicyclo[5.4.0]undecene and tetramethylguanidine, which make it possible to obtain DAA with high (*Z*)/(*E*) ratios, were found to be more promising in some cases than alkali metal derivatives, NaH, Bu^tOK, or $Pr^i{}_2NLi$,[5] whose use results in formation of nonidentified by-products that poison the catalyst during hydrogenation. Besides, in this case, purification of DAA requires the use of medium-pressure LC, which is a labor-consuming method. When nitrogen-containing bases are employed, chemical purification of DAA is much easier.

In the present work, we have shown that in most cases, the Wittig—Horner reaction of *N*-carbobenzoxy-2-(dimethoxyphosphinyl)glycine (**1**) with ArCHO (**2**) can be successfully accomplished using low-cost and available Et_3N as the base. The reaction yields 3-aryl-2-(carbobenzoxyamino)acrylates (**3**) with high (*Z*)/(*E*) ratios (>10 : 1). Facile preparative-scale methods for the synthesis of isomerically pure (*Z*)-**3** have been developed.

Results and Discussion

Until the present study aliphatic tertiary amines without additives were thought to be inefficient as bases in the Wittig—Horner reaction, and they were used only in combination with metal salts.[6,7]

We were surprised to find out that the reaction of phosphonyl derivative of glycine **1** with aromatic aldehydes **2a—q** in the presence of Et_3N smoothly proceeds at ambient temperature in MeOH or THF without any additives (Scheme 1, Table 1). In some

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Table 1. Methyl 3-aryl-2-(carbobenzoxyamino)acrylates[a]

Product	Ar	Base	Solvent	M.p./°C	Yield (%)
(*Z*)-**3a**	3,5-$F_2C_6H_3$	Et_3N	MeOH	118—119[b]	82
(*Z*)-**3b**	3,5-$(CF_3)_2C_6H_3$	Et_3N	MeOH	170—171[c]	80
(*Z*)-**3c**	2-FC_6H_4	Et_3N	MeOH	75—76[d]	73
(*Z*)-**3d**	3-FC_6H_4	Et_3N	MeOH	59—60[d]	49
(*Z*)-**3e**	4-FC_6H_4	Et_3N	MeOH	92—93[e]	85
(*Z*)-**3f**	2-Thienyl	Et_3N	MeOH	114—116[c]	62
(*Z*)-**3g**	3-Thienyl	Et_3N	MeOH	86—88[c]	59
(*Z*)-**3h**	1-Naphthyl	Et_3N	MeOH	97—98[f]	27
(*Z*)-**3j**	2-Naphthyl	Et_3N	THF	121—123[f]	67
(*Z*)-**3k**	4-$CF_3C_6H_4$	Et_3N	THF	75—76[d]	78
(*Z*)-**3l**	3-Pyridyl	Et_3N	THF	94—95[e]	74
(*Z*)-**3m**	3,5-$(MeO)_2C_6H_3$	Et_3N	THF	96—98[e]	63
(*Z*)-**3n**	3-$MeOC_6H_4$	Et_3N	THF	68—70[g]	57
(*Z*)-**3o**	3-(1-*tert*-Butoxycarbonyl)-indolyl	Bu^tOK	THF	104—106[e]	49
(*Z*)-**3p**	4-$MeOC_6H_4$	K_2CO_3	MeCN	67—68[h]	28
(*Z*)-**3q**	2-$MeOC_6H_4$	NaH	THF	56—57[d,i]	
(*E*)-**3q**	2-$MeOC_6H_4$	NaH	THF	101—102[d,i]	

[a] The yields are based on the isolated analytically pure products. The ^1H NMR spectra and the results of elemental analyses correspond to the structures of the obtained compounds. [b] MeOH—H_2O (3 : 1). [c] MeOH. [d] Et_2O—hexane (1 : 1). [e] Benzene—hexane (1 : 1). [f] Benzene. [g] Benzene—hexane (1 : 2). [h] Et_2O—hexane (2 : 1). [i] The isomers were separated by column chromatography on SiO_2 (Et_2O—hexane, 1 : 1).

cases, the reaction is accompanied by heat evolution. In the reactions involving aldehydes **2a,b**, products crystallizing from the reaction mixture are formed within 20 min. In other cases, it takes longer (up to 2—10 days) to achieve 80 % degree of aldehyde conversion. In these reactions, THF is preferred as the solvent, since in MeOH, partial reduction of compound **1** is observed.[5]

The course of the reaction was monitored by TLC (SiO_2; PhH—AcOEt, 15 : 1). During the reaction of compound **1** with aldehydes **2** in the presence of Et_3N two new compounds **3** in a ratio of >10 : 1 (according to semiquantitative visual evaluation by TLC) are formed. The (*Z*)-configuration was assigned to the major product based on the following facts: (1) (*E*)-**3m** and (*E*)-**3q** undergo epimerization in a solution of MeOH—$CHCl_3$ in the presence of activated carbon and Et_3N (see Ref. 5) yielding the corresponding (*Z*)-isomers in a substantial excess; (2) condensation of alkoxyphosphorylglycines with aldehydes gives excessive amounts of (*Z*)-isomers in all cases.[4,5]

After treating the reaction mixture with water, one recrystallization is sufficient in most cases to obtain preparative-scale quantities (5—10 g) of isomerically and chemically pure (*Z*)-**3a—n**. The yields and characteristics of the prepared compounds are presented in Table 1. Conditions, in which the reactions were carried out and the final products were isolated, were not optimized.

To illustrate the advantage of using Et_3N instead of Bu^tOK, we compared the reactions of condensation of **1** with **2m** carried out in the presence of these two bases. In the case of Et_3N, the usual workup of the reaction mixture immediately afforded the crystalline product, despite the fact that a considerable quantity of starting **2m** was recovered. In the case of Bu^tOK, the final reaction mixture contained only traces of **2m**; however, its workup yielded a viscous noncrystallizing oil that contained a larger proportion of the (*E*)-isomer than the product obtained in the previous experiment. The proportion of the (*E*)-isomer appreciably decreased when the mixture was heated in the presence of activated carbon and Et_3N in MeOH, but, nevertheless, we were not able to isolate pure (*Z*)-**3m** by crystallization. This may be due to the presence of some impurities that cannot be detected by TLC.

The reaction of **1** with **2o** also occurs in a THF—Et_3N mixture, but the degree of conversion of **2o** is low (approximately 50 %). When Bu^tOK in THF was used, virtually complete conversion of **2o** was attained over a period of 10 min. An analytically pure sample of (*Z*)-**3o** was obtained only after chromatographic purification (SiO_2; PhH—AcOEt, 15 : 1) repeated two times and subsequent crystallization of the amorphous material.

The reaction of **1** with **2p** does not occur in the presence of Et_3N, Bu^tOK, or NaH. The required product (*Z*)-**3p** was prepared in a relatively low yield when the reaction was carried out in boiling MeCN in the presence of K_2CO_3. Under these conditions, the (*Z*)/(*E*) ratio was lower than those in the reactions carried out with Et_3N; however, it was ample for isolation of the final product by crystallization.

Experimental

Reagents (produced by Aldrich and Fluka) were used without additional purification. Et_3N was distilled over solid NaOH, THF was distilled over $NaPh_2CO$, and the other reagents were used without purification. TLC was carried out on SiO_2 plates (Merck 60 F254). For column chromatography, silica gel 60 (Merck) was used. Melting points were not corrected. ^1H NMR spectra were recorded on a Bruker WP-200 spectrometer.

Methyl 2-dimethoxyphosphinyl-2-(carbobenzoxyamino)acetate (1) was prepared from methyl 2-carbobenzoxyamino-2-methoxyacetate[8] by a modification of the known procedure;[4] the reaction was carried out in boiling benzene instead of toluene at 70 °C. Yield 64 %, m.p. 78—80 °C (Ref. 4: m.p. 80 °C).

1-*tert*-Butoxycarbonyl-3-formylindole (2o). A mixture of 3-formylindole (1 g, 6.87 mmol), di-*tert*-butyl dicarbonate (1.6 g, 7.33 mmol), finely grinded K_2CO_3 (0.3 g, 2.17 mmol), and 20 mL of MeCN were stirred for 4 h at ambient temperature, then an additional 0.3 g of K_2CO_3 was added, and the mixture was stirred for an additional 2 h. The course of the reaction was monitored by TLC (SiO_2, $CHCl_3$). The reaction mixture was diluted with water, and the crystalline precipitate was filtered off, thoroughly washed with water, and dried in air to give **2o**, yield 1.6 g (95 %), m.p. 125.5—126.5 °C. Recrystallization from hot ethanol gave 1.4 g (83 %) of chromatographically pure **2o** with m.p. 127.5—128.5 °C (Ref. 8: m.p. 124—125 °C).

Methyl (*Z*)-3-aryl-2-(carbobenzoxyamino)acrylates (*Z*)-(3a—n). ***General procedure of the synthesis using*** **Et_3N.** A twofold molar excess of Et_3N was added in one portion to a stirred solution of **1** and aldehyde (in a molar ratio of 1 : 1) in MeOH or THF. Normally 1—2 mL of the solvent per mmol of starting **1** was taken. The course of the reaction was monitored by TLC (SiO_2; PhH—AcOEt, 15 : 1). When approximately an 80—100% degree of aldehyde conversion was achieved, the reaction mixture was diluted with water. If a precipitate formed, it was filtered off, washed with water, dried in air, and recrystallized. Otherwise, the product was extracted with benzene, the extract was successively washed with concentrated aqueous $NaHCO_3$, concentrated aqueous NaCl, and 2 *M* aqueous HCl, dried with $MgSO_4$, and concentrated, and the residue was recrystallized. Drying in air sufficed to obtain analytically pure samples. Only in the case of (*Z*)-**3m** was formation of a relatively stable solvate with benzene detected; the solvate was decomposed by heating *in vacuo* at 64 °C over paraffins. Yields and melting points of the synthesized compounds are presented in Table 1.

Methyl (*Z*)-3-(1-*tert*-butoxycarbonylindol-3-yl)-2-(carbobenzoxyamino)acrylate (*Z*)-3o. Bu^tOK (3.3 g, 30 mmol) was added in one portion with stirring to a mixture of **1** (8 g, 24.2 mmol), **2o** (6 g, 24.5 mmol), and 30 mL of THF, cooled to 0 °C. The cooling bath was removed, and the mixture was stirred for 2.5 h. After that, 2.4 mL of AcOH was added, and the mixture was diluted with water. The product was extracted with benzene, the extract was processed as described above. The viscous yellowish product was purified on a column packed with SiO_2 (300×50 mm) using PhH—AcOEt, 15 : 1 as the eluent. Fractions enriched in (*Z*)-**3o** were combined and once again chromatographed. The product was isolated as a thick oil, which partly crystallized on prolonged storage. It was entirely crystallized by triturating with hexane, filtered off, and washed with hexane to give 6.1 g (55.3 %) of compound (*Z*)-**3o**, m.p. 102—105 °C. The whole product was placed in 60 mL of hexane, heated to boiling, and dissolved by adding a minimum amount of benzene. The precipitate formed after cooling the solution was filtered off, washed with hexane, and dried in air to give 5.4 g (49 %) of pure (*Z*)-**3o**.

Methyl (*Z*)-2-carbobenzoxyamino-3-(4-methoxyphenyl)acrylate (*Z*)-3p. A mixture of **1** (10 g, 30.2 mmol), **2p** (3.7 mL, 4.4 g, 32.3 mmol), K_2CO_3 (12.6 g, 91.3 mmol), and 30 mL of MeCN was boiled with stirring for 2 h. The usual workup gave a yellowish thick oil, which was dissolved in a boiling mixture of ether with hexane (2 : 1). The crystalline precipitate formed after cooling the solution was filtered off, washed with hexane, and dried to give (*Z*)-**3p**, yield 4 g (38.8 %). Repeated recrystallization yielded 2.8 g (28 %) of analytically pure (*Z*)-**3p**.

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References

1. I. Ojima, N. Clos, and C. Bastos, *Tetrahedron*, 1989, **45**, 6901.
2. G. Zassinovich, G. Mestroni, and S. Gladiali, *Chem. Rev.*, 1992, **92**, 1051.
3. M. J. Burk, J. E. Feaster, W. A. Nugent, and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
4. U. Schmidt, A. Lieberknecht, and J. Wild, *Synthesis*, 1984, 53.
5. U. Schmidt, H. Griesser, V. Lietenberger, A. Lieberknecht, R. Mangold, R. Meyer, and B. Riedl, *Synthesis*, 1992, 487.
6. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sasaki, *Tetrahedron Lett.*, 1984, **25**, 2183.
7. M. W. Rathke and M. Nowak, *J. Org. Chem.*, 1985, **15**, 2625.
8. U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863.
9. L. Wackerle and I. Ugi, *Synthesis*, 1975, 589.

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