molecules

Captodative Formyl Enamines in a New Synthesis of Tertiary α-Amino Esters

Alexandre Yu. Rulev*, Lyudmila I. Larina and Mikhail G.Voronkov

A.E.Favorsky Institute of Chemistry, Siberian Division of the Russian Academy of Sciences,

1, Favorsky Str., Irkutsk 664033, Russia. Tel. +7 (3952)-460-685, Fax +7 (3952)-396-046.

* Author to whom correspondence should be addressed; e-mail rulev@irioch.irk.ru

Abstract: A strategy to create the –CH(NR$_2$)CO- moiety from captodative formyl enamines was successfully applied to the synthesis of tertiary α-amino esters.

Keywords: Captodative formyl enamine, dialkyl phosphite, α-amino ester.

Introduction

Modern strategy in organic synthesis is based on the use of multifunctional and relatively simple building blocks [1]. In the design of diverse complicated molecules, it is useful to proceed from compounds with so-called "compositional functional groups" [2]. The "symbiosis" of several functional groups at the same carbon center is know to lead sometimes to a substantial change in the chemical properties of the substrate (see, for example, reference [3]).

N,N-Disubstituted α-formyl enamines are compounds of particular interest. Though different syntheses of these derivatives were developed some years ago [4-7], little is known so far about their chemical behavior. Two important features characterize this type of compounds:

a) They can be treated either as α,β-unsaturated carbonyl systems with a tertiary amino function or as α-formyl enamines; therefore, this multifunctional pattern can lead to surprising and unexpected reactions;

   b)   In view of the presence of the tertiary amino group and of the double bond at the α-position of the carbonyl one, these derivatives can readily provide access to various biologically important products and natural analogues.

These features triggered our interest in the chemistry of N-protected captodative formyl enamines, particularly in their reactivity toward nucleophiles. According to the NMR study, the most electrophilic sites of α-formyl enamines (**1**) are the carbonyl and the α-carbon atoms of the olefin atoms [8]. However, the β-position of both the terminal and internal double bond in α-ketoenamines also sometimes shows an electrophilic character [9,10].

To our surprise, the treatment of α-formyl enamines (**1**) with soft nucleophiles does not lead to the expected 1,4- and 1,2-addition products. In all cases a cascade of transformations occurs to give finally the derivatives of α-amino acids. Thus, we have found that the enamines (**1**) react with alkyl- or arylthiols to give the corresponding thiol esters in good yield [11]. Following this discovery we have been interested in further developing methodology which would provide easy access to the -CH(NR$_2$)C(O)- fragment. Our attention was drawn to the tertiary α-amino esters which have a particular significance because of their varied pharmacological properties [12]. Recently, we have described an important route for the preparation of N,N-disubstituted α-amino esters by treatment of the α-formyl enamines (**1**) with dialkyl phosphites (**2**) [13]. In this paper, synthetic and mechanistic aspects of this unusual transformation are considered in more detail.

Results and Discussion

The reaction of α-formyl enamines (**1**) with dialkylphosphites (**2**) was performed at ambient temperature, without solvent and in the presence of a concentrated solution of sodium alkoxide in a manner similar to that described for α,β-unsaturated carbonyl compounds [14-16]. In contrast to analogous reactions involving simple α,β-unsaturated carbonyl derivatives and other captodative olefins, α-formyl enamines (**1**), under the action of dialkylphosphites (**2**), undergo an unusual transformation leading to tertiary α-amino esters in 30-40% yield (Scheme 1). The moderate yields may be explained by the polymerization of the initial substrate (**1**) which occurs under strong basic conditions. It should be noted that no reaction is observed in the absence of the catalyst.

Scheme 1
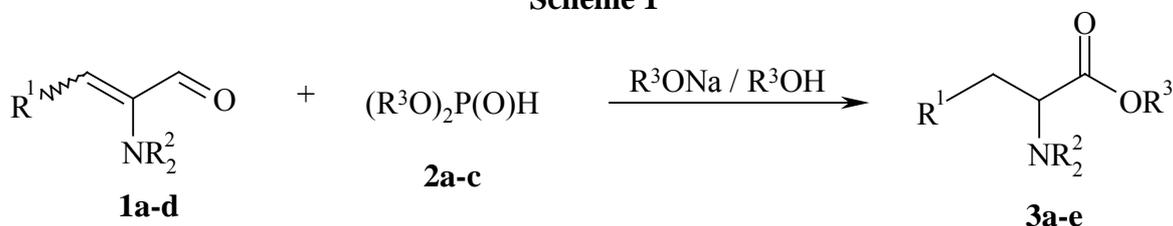
1 : (**a**) R^1 = Me, NR_2^2 = N(CH$_2$)$_5$; (**b**) R^1 = Me, NR_2^2 = N(CH$_2$CH$_2$)$_2$O;
    (**c**) R^1 = Pr, NR_2^2 = N(CH$_2$)$_5$; (**d**) R^1 = Ph, NR_2^2 = NEt$_2$.
2 : (**a**) R^3 = Me; (**b**) R^3 = Et; (**c**) R^3 = Pr.
3 : (**a**) R^1 = Me, NR_2^2 = N(CH$_2$)$_5$, R^3 = Me; (**b**) R^1 = Me, NR_2^2 = N(CH$_2$)$_5$, R^3 = Et;
    (**c**) R^1 = Me, NR_2^2 = N(CH$_2$CH$_2$)$_2$O, R^3 = Me; (**d**) R^1 = Pr, NR_2^2 = N(CH$_2$)$_5$, R^3 = Me;
    (**e**) R^1 = Ph, NR_2^2 = NEt$_2$, R^3 = Et.

It has been found that the structural peculiarities of substrates (**1**) have no influence on the results. The desired esters (**3**) were successfully obtained from the substrates (**1**) bearing both alkyl (Me, Pr) and aryl (Ph) substituent at the β-position. The reaction course is also independent of the structure (cyclic or acyclic) and basicity (high or moderate) of the amine moiety.

In order to achieve the best yields in the preparation of the target esters (**3**) we have tested the behavior of the enamines (**1**) under milder conditions. It has been found that the use of less basic triethylamine instead of sodium alkoxide as a catalyst in the reaction of the substrate (**1d**) with dimethyl phosphite (**2a**) affords a complex mixture, from which the expected α-amino ester (**3**) could not be isolated. Since the increase in nucleophilicity should favor the addition at the carbonyl center, it was reasonable to propose the use of more effective P-nucleophiles. It is known that dialkylphosphine oxides easily react with various aldehydes without catalyst leading to the corresponding 1,2-adducts [17]. However, no reaction occurs when the enamine (**1d**) is treated with an equimolar quantity of di(β-phenyl)ethyl phosphine oxide (**4**); the signals of the unchanged starting materials are detected by NMR spectroscopy even after leaving the reaction mixture for a day at room temperature. Therefore, we conclude that the use of a concentrated solution of sodium alkoxide is necessary to achieve satisfactory transformations.

The results obtained as well as some earlier published data suggest a possible mechanism of this process that easily explains the formation of the target esters (**3**). A similar sequence of transformations has previously been described for the synthesis of thiol esters from the same substrates (**1**) [11]. A likely mechanism of the formation of the esters (**3**) is presented in Scheme 2.

Scheme 2.
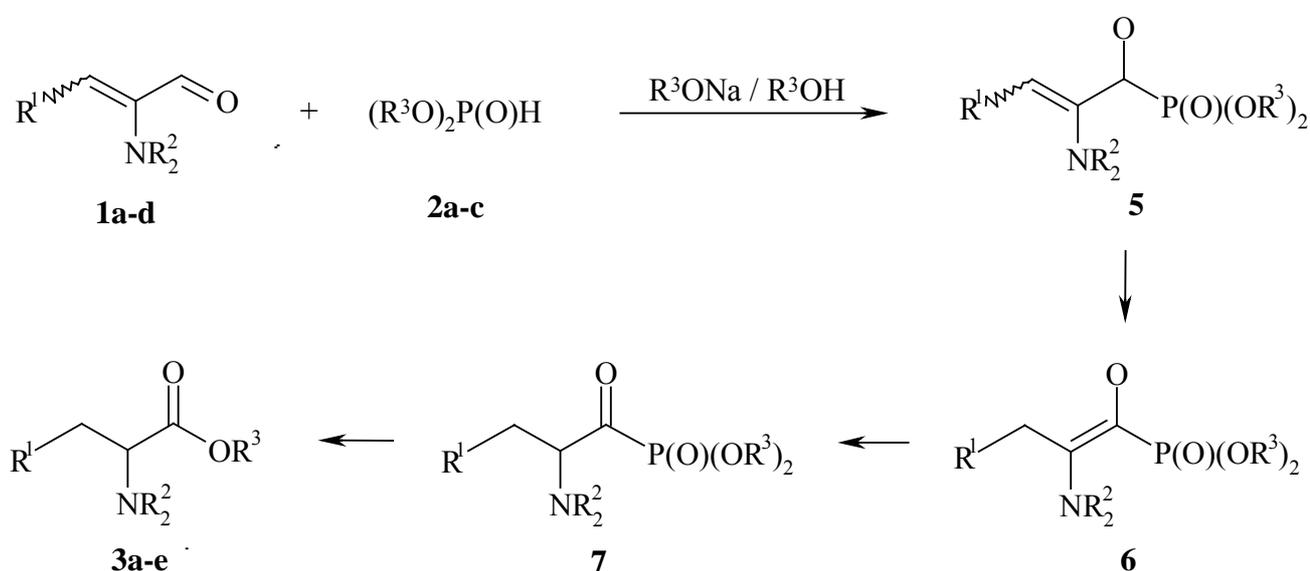
According to this scheme, the first step involves a nucleophilic attack of the sodium salt of dialkyl phosphite on the carbonyl carbon of the starting enamine (**1**). The unstable 1,2-adduct (**5**) undergoes an isomerization to the thermodynamically more stable enol (**6**), followed by the immediate transformation into the α-keto-β-aminophosphonate (**7**). In our opinion, this is a key step in the

cascade of reactions. The α-ketophosphonates (**7**) are known to undergo a very easy cleavage of the carbon-phosphorus bond under the action of nucleophiles – amines or alcohols [18,19]. In a similar manner the phosphonate (**7**) gives the final desired product (**3**).

We tried to confirm the postulated mechanism by isolating one of the intermediates as a stable derivative. In a recent study of the reaction of α-formyl enamines (**1**) with thiols, we have reported that all attempts to collect evidence for this sequence of transformations failed. The use of alkylthiotrimethylsilane in the reaction with the enamine (**1**) under both non-catalytic and catalytic conditions resulted in either the starting materials or the complex mixture of non-identified products, respectively [11]. In contrast, the similar reaction of enamine (**1d**) with dimethyl(trimethylsilyl)phosphite (**8**) [20, 21] under thermal or microwave activation was effective (Scheme 3).

Scheme 3.
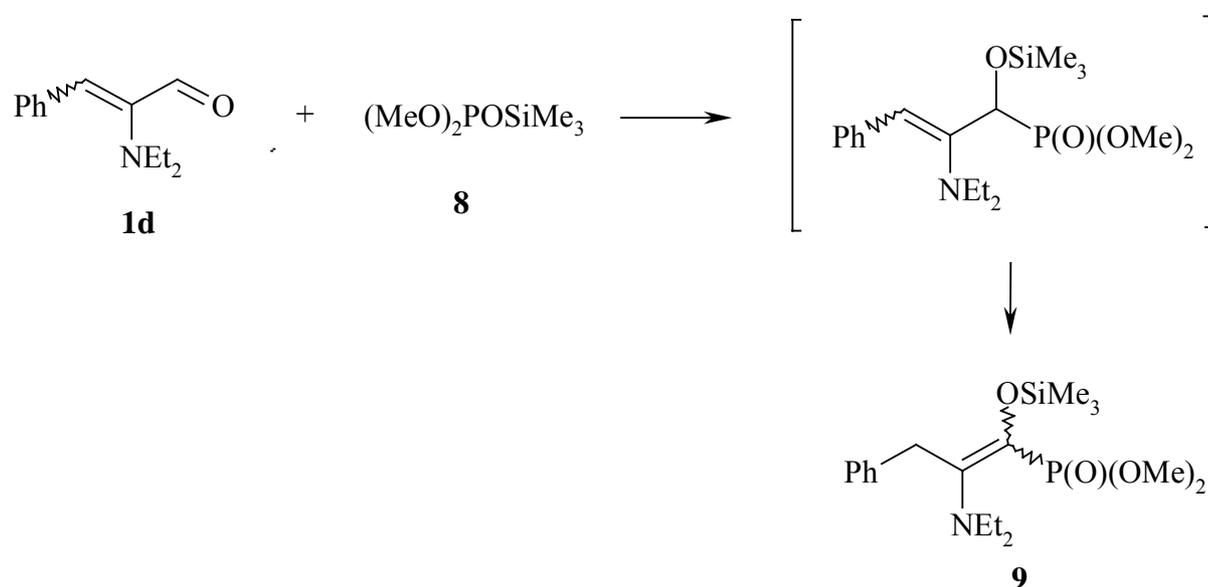
The isolation of silyl enol ether (**9**) in good yield strongly supports the suggested mechanism. These results indicate that the dialkyl phosphites (**2**) provide a vicarious assistance to the alcohol addition. Indeed, when the enamine (**1a**) was treated with an equimolar amount of dipropylphophite (**2c**) in the presence of a methanolic solution of sodium methoxide under optimized conditions methyl 2-piperidinopropionate (**3a**) was formed mainly. To our knowledge, the first example of vicarious nucleophilic addition has only recently been reported [22].

Conclusions

From our studies of captodative formyl enamines, we can conclude that the reaction of these compounds with phosphite derivatives might provide a new and convenient approach to tertiary α-

amino acid derivatives. Further development of this remarkable methodology will be reported in due course.

Experimental

General

^{1}H- and ^{13}C-NMR spectra were obtained for CDCl$_3$ solutions on a Bruker DPX-250 NMR spectrometer operating at 400 and 100 MHz respectively. GC/MS Analyses (EI, 70eV) were performed on a Hewlett-Packard HP 5971A instrument. IR spectra (thin film) were recorded on a Specord 75-IR spectrometer. The starting reagents (**1a-d**) were obtained from the corresponding α-halo-α,β-unsaturated aldehydes according to our previously described method [6,7].

General procedure for the preparation of N,N-disubstituted α-amino esters (**3a-e**).

A concentrated solution of the corresponding sodium alkoxide (10-15 drops) was added to the mixture of equimolar amounts (5-10 mmol) of α-formyl enamine (**1**) and dialkylphosphite (**2**). The reaction mixture was kept at rt for 2 h and then distilled *in vacuo* to afford a mixture of esters (**3**) and the initial phosphite (**2**). The latter mixture was subjected to preparative gas chromatography or was treated with dry HCl in anhydrous Et$_2$O followed by HCl elimination with a solution of NaHCO$_3$ to give pure target product (**3**). In this manner the following compounds were prepared:

Methyl 2-piperidinobutanoate (**3a**): Yield 37 %; ^{1}H-NMR δ: 0.87 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.35-1.60 (m, 6H, CH$_2$ β,γ–CH$_2$ piperidine), 1.60-1.80 (m, 2H, CH$_3$C̲H̲$_2$), 2.40-2.55 (m, 4H, α–CH$_2$ piperidine), 3.01 (dd, *J* = 8.6, 6,2 Hz, 1H, CHN), 3.66 (s, 3H, OCH$_3$); ^{13}C NMR δ: 10.82 (CH$_3$), 22.62 (CH$_2$), 24.71, 26.51 (CH$_2$, piperidine), 50.83 (NCH$_2$), 50.91 (OCH$_3$), 70.20 (CHN), 173.04 (C=O); IR cm^{-1}: 1720 (C=O); MS (m/z): 185 (M$^+$, 1), 126 (100); Calcd. for C$_{10}$H$_{19}$NO$_2$ (%): C 64.83, H 10.34, N 7.56; Found (%): C 65.02, H 10.29, N 7.68.

Ethyl 2-piperidinobutanoate (**3b**): Yield 35 %; ^{1}H-NMR δ: 0.90 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.27 (t, *J* = 7.1 Hz, 3H, C̲H̲$_3$CH$_2$O), 1.35-1.60 (m, 6H, β,γ–CH$_2$ piperidine), 1.65-1.85 (m, 2H, CH$_3$C̲H̲$_2$), 2.40-2.55 (m, 4H, α–CH$_2$ piperidine), 3.04 (dd, *J* = 8.6, 6,2 Hz, 1H, CHN), 4.15 (q, *J* = 7.1 Hz, 2H, CH$_3$C̲H̲$_2$O); ^{13}C-NMR δ: 10.84 (CH$_3$), 14.63 (CH$_3$), 22.62 (CH$_2$), 24.71, 26.46 (CH$_2$, piperidine), 50.88 (NCH$_2$), 59.97 (OCH$_2$), 70.20 (CHN), 172.41 (C=O); IR cm^{-1}: 1718 (C=O); MS (m/z): 199 (M$^+$, 1), 126 (100); Calcd. for C$_{11}$H$_{21}$NO$_2$ (%): C 66.29, H 10.62, N 7.03; Found (%): C 65.85, H 10.72, N 7.43.

Methyl 2-morpholinobutanoate (**3c**): Yield 32 %; ^{1}H-NMR δ: 0.87 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.55-1.75 (m, 2H, CH$_2$), 2.45-2.60 (m, 4H, N(CH$_2$)$_2$), 3.00 (dd, *J* = 8.4, 6,6 Hz, 1H, CHN), 3.60-3.70 (m, 4H, O(CH$_2$)$_2$), 3.65 (s, 3H, OCH$_3$); ^{13}C-NMR δ: 10.58 (CH$_3$), 22.11 (CH$_2$), 50.12 (NCH$_2$), 51.05 (OCH$_3$),

67.36 (OCH$_2$), 69.64 (CHN), 172.51 (C=O); IR cm^{-1}: 1730 (C=O); MS (m/z): 187 (M$^+$, 1), 128 (100); Calcd. for C$_9$H$_{17}$NO$_3$ (%): C 57.73, H 9.15, N 7.48; Found (%): C 57.38, H 9.36, N 7.75;.

Methyl 2-piperidinohexanoate (**3d**): Yield 31 %; ^{1}H-NMR δ: 0.85 (t, *J* = 7.1 Hz, 3H, CH$_3$), 1.20-1.60 (m, 12H, (CH$_2$)$_3$, β,γ–CH$_2$ piperidine), 2.40-2.55 (m, 4H, α–CH$_2$ piperidine), 3.07 (dd, *J* = 8.8, 6,0 Hz, 1H, CHN), 3.65 (s, 3H, OCH$_3$); ^{13}C-NMR δ: 14.06 (CH$_3$), 22.70, 24.79, 26.60, 28.67, 29.37 (CH$_2$), 50.91 (OCH$_3$), 50.92 (NCH$_2$), 68.66 (CHN), 173.23 (C=O); IR cm^{-1}: 1728 (C=O); MS (m/z): 213 (M$^+$, 1), 154 (100); Calcd. for C$_{12}$H$_{23}$NO$_2$ (%): C 67.57, H 10.87, N 6.57; Found (%): C 67.83, H 10.55, N 6.85.

Ethyl 2-diethylamino-3-phenylpropiolate (**3e**): Yield 30 %; ^{1}H-NMR δ: 1.00 (t, *J* = 7.1 Hz, 6H, CH$_3$CH$_2$N), 1.14 (t, *J* = 7.1 Hz, 3H, CH$_3$CH$_2$O), 2.53 (dq, *J* = 13.2, 7.0 Hz, 2H, CH$_3$CH$_2$N), 2.77 (dq, *J* = 13.2, 7.1 Hz, 2H, CH$_3$CH$_2$N), 2.87 (dd, *J* = 13.4, 6.2 Hz, 1H, CH$_2$), 3.05 (dd, *J* = 13.4, 8.6 Hz, 1H, CH$_2$), 3.60 (dd, *J* = 8.6, 6,2 Hz, 1H, CHN), 4.05 (dq, *J* = 7.1, 3.8 Hz, 2H, CH$_3$CH$_2$O), 7.15-7.30 (m, 5H, C$_6$H$_5$); ^{13}C-NMR δ: 13.94 (CH$_3$), 14.39 (CH$_3$), 36.47 (CH$_2$), 44.65 (NCH$_2$), 60.03 (OCH$_2$), 65.17 (CHN), 126.24, 128.22, 129.38, 138.96 (C$_6$H$_5$), 172.74 (C=O); IR cm^{-1}: 1728 (C=O); MS (m/z): 249 (M$^+$, 1), 176 (100), 158 (61), 130 (27), 91 (33), 56 (34); Calcd. for C$_{15}$H$_{23}$NO$_2$ (%): C 72.25, H 9.30, N 5.62; Found (%): C 71.66, H 9.12, N 5.98.

Reaction of enamine (**1d**) *with dimethylphosphite* (**2c**) *in the presence of triethylamine*.

The reaction of enamine (**1d**) with dimethylphosphite (**2a**) was carried out according to the general procedure except that an equimolar amount of triethylamine was used instead of sodium methoxide. Only decomposition of the starting material to unidentified products occurred.

Reaction of enamine (**1a**) *with dipropylphosphite* (**2c**).

Enamine (**1a**) (1.5 g, 10 mmol) and dipropylphosphite (**2c**) (1.6 g, 10 mmol) were reacted as indicated in the general procedure using sodium methoxide in methanol as a catalyst. The reaction mixture was distilled to give 1.6 g of a mixture consisting mainly of ester (**3a**) and starting phosphite (**2c**).

Reaction of enamine (**1d**) *with di(β-phenyl)ethylphosphine oxide* (**4**).

A mixture of the enamine (**1d**) (106 mg, 0.52 mmol) and phosphine oxide (**4**) (135 mg, 0.55 mmol) was placed in a tube. The tube was then subjected to microwave irradiation in a commercial microwave oven (700 W) for 5 min. The cooled tube was opened and the contents were analysed by NMR: only the signals of the unchanged starting materials were detected.

*Reaction of enamine (**1d**) with dimethyl(trimethylsilyl) phosphite (**8**).*

a) To cooled enamine (**1d**) (0.20 g, 1.0 mmol) was added dimethyl(trimethylsilyl)phosphite (**8**) (0.18 g, 1.0 mmol) under a dry argon atmosphere and reaction mixture was heated for 2 h at 95°C. The pure ether (**9**) was isolated by vacuum distillation: b.p. 120-121°C (1 mm); Yield 0.30 g (78 %); ^{1}H-NMR δ: 0.22 (s, 9H, $(CH_3)_3Si$), 0.85 (t, *J* = 7.0 Hz, 6H, $\underline{CH_3}CH_2N$), 3.08 (q, *J* = 7.0 Hz, 4H, $CH_3\underline{CH_2}N$), 3.71 (d, *J* = 11.0 Hz, 6H, CH_3O), 4.02 (s, 2H, Ph$\underline{CH_2}$), 7.10-7.40 (m, 5H, C_6H_5); ^{13}C-NMR δ: 0.50 (CH_3Si), 13.53 (CH_3), 35.40 ($PhCH_2$), 43.69 (NCH_2), 52.07 (d, *J* = 5.8 Hz, OCH_3), 125.94, 128.12, 128.88, 139.36 (C_6H_5), 147.70, 148.19 (C=C); ^{31}P-NMR δ: 20.05; IR cm^{-1}: 1686 (C=C); . Calcd. for $C_{18}H_{32}NO_4PSi$ (%): C 56.08, H 8.37, N 3.63, P 8.03, Si 7.29; Found (%): C 56.67, H 8.53, N 3.65, P 7.79, Si 7.05.

b) A mixture of substrate (**1d**) (0.30 g, 1.5 mmol) and dimethyl(trimethylsilyl)phosphite (**8**) (0.27 g, 1.5 mmol) was placed in a tube. The tube was then subjected to microwave irradiation in a commercial microwave oven (700 W) for 2 min intervals. This process was repeated 5 times (i.e., total of 10 min). The cooled tube was opened and the contents were distilled to give the same ether (**9**) in 52% yield.

References and Notes

1. Tietze, L.F., Beifuss U. Sequential transformations in organic chemistry: a synthesis strategy with a future. *Angew. Chem. Int. Ed. Engl.* **1993**, *105*, 131-163.
2. De Meijere, A. Fine chemistry with small ring – cyclopropyl compounds for efficient synthesis. In *New Aspects of Organic Chemistry*, vol. II, Yoshida, Z; Ohshiro, Y., Eds, Kodansha: Tokyo, **1992**, 181-213.
3. Rulev, A.Yu. Haloalkenes activated by geminal groups in reactions with N-nucleophiles. *Russ. Chem. Rev.* (*Engl. Transl.*) **1998**, *67*, 279-293.
4. Duhamel, L., Plé, G., Commare P. Action des réactifs de Grignard sur les ènediamines formylées. Voie d'accès aux α-aminoaldehydes α,β-éthyléniques. *C. R. Acad. Sci.* **1974**, *278*, 1113-1116.
5. Klein, J.L., Combret J.C. Reaction des amines secondaires avrc les aldehydes α,β-dibromés. Préparation d'α,β-diaminoaldehydes dérivés du cinnamaldehyde et nouvelle voie d'accès aux diamino-1,2-éthylenes. *Bull. Soc. Chim. Fr., Part 2,* **1983**, 28-32.
6. Keiko, N.A., Rulev, A.Yu., Kalikhman, I.D., Voronkov, M.G. A new synthetic route to 2-dialkylamino-2-alkenals. *Synthesis* **1989**, 446-447.
7. Rulev, A.Yu., Keiko, N.A., Voronkov, M.G. Reactions of α-halo-α,β-unsaturated aldehydes with secondary amines. *Russ. Chem. Bull.* (*Engl. Transl.*) **1996**, *45*, 125-128.
8. Rulev, A.Yu., Mokov, A.S., Krivdin, L.B., Keiko, N.A., Voronkov, M. G. N,N-Disubstituted α-amino-α,β-unsaturated aldehydes and their derivatives : ^{1}H and ^{13}C NMR study. *Magn. Res. Chem.* **1997**, *35*, 533-537.
9. Kucklander, U. Enaminones as synthones. In *The Chemistry of enamines*, Z Rappoport, Ed., John Wiley & Sons: New York, **1994**, 523-636.

10. Polozov, G.I., Tishchenko, IG. The chemistry of α-enaminoketones. *Vestnik Beloruss. Gos. Univ., Ser. II*, **1984**, 3-15 (*Russ*).

11. Rulev, A.Yu., Larina, L.I., Voronkov, M.G. New Convenient Access to Thioesters of α-Amino Acid from N,N-Disubstituted 2-Amino-2-Alkenals. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1567-1570.

12. See, for example: (a) Katritzky, A.R., Urogdi, L., Mayence, A. The chemistry of N-substituted benzotriazoles. Part 23. Synthesis of tertiary α-amino esters, *Synthesis* **1989**, 323-327; (b) Chruma, J.J., Sames, D., Polt, R. General method for the synthesis of N-methyl amino acids and N-alkyl amino esters from O'Donnell's Schiff Bases. *Tetrahedron Lett*. **1997**, *38*, 5085-5086 and references therein.

13. Rulev, A.Yu., Larina, L.I., Voronkov, M.G. Transformations des énamines α-formylées: Synthèse d'α-amino esters N,N-disubstitués. *Tetrahedron Lett*. **2000**, *41*, 10211-10214.

14. Pudovik, A.N., Zimin, M.G., Sobanov, A.A. Reaction of acrolein with the sodium salts of dialkyl phosphites. *Zh. Obshch. Khim.* **1978**, *48*, 487-489 (*Russ*).

15. Pudovik, A.N. Addition of dialkyl phosphites to unsaturated compounds. III. New synthesis of α-keto phosphonic esters. *Zh. Obshch. Khim.* **1952**, *22*, 462-467 (*Russ*).

16. Pudovik, A.N., Kitaev,Yu.P. Addition of dialkyl phosphites to unsaturated aldehydes. New method of synthesis of unsaturated α-hydroxy phosphonic esters. *Zh. Obshch. Khim.* **1952**, *22*, 467-473 (*Russ*).

17. See, for example: (a) Kabachnik, M.I., Tsvetkov, E.N. Dialkylphosphinous acids (secondary phosphine oxides). *Izv. Akad. Nauk SSSR. Ser. Khim*. **1963**, 1227-1232 (*Russ*); (b) Kleiner, H-J. Preparation and reactions of dimethylphosphine oxide. *Liebigs Ann. Chem*. **1974**, 751-764.

18. Pudovik, A.N., Gazizov, T.H., Pashinkin, A.P. Breaking of a phosphorus-carbon bond in chloro-substituted esters of acetophosphonic acids. *Zh. Obshch. Khim.* **1968**, *38*, 2812 (*Russ*).

19. Pashinkin, A.P., Gazizov, T.H., Pudovik, A.N. Breaking the phosphorus-carbon bond of α-oxo phosphonates. *Zh. Obshch. Khim.* **1970**, *40*, 28-30 (*Russ*).

20. Li Z.; Zhao, Y.; Zhang, J. The synthesis of trimethylsiloxyallyl phosphonates. *J. Cent. China Norm. Univ. Natur. Sci*. **1991**, *25*, 62-65.

21. Arbuzov, B.A., Tudrii G.A. 1,2-Addition of dimethyl trimethylsilyl phosphite to benzalacetone. *Izv. Akad. Nauk. Ser. Khim*., **1981**, 467 (*Russ*).

22. Trofimov B.A., D'yachkova S.G., Nikitina E.A., Gusarova N.K. Dimerization of (alkylthio)-chloroacetylenes initiated by sodium sulfite. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2000**, *165*, 191-195.

Sample Availability: Samples are available from the authors.