ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении 71, №4, 2018 Chemical Journal of Armenia

UDC 547.787

EVALUATION OF THE DEHYDRATING PROPERTIES OF SOME SILILATING AGENTS IN THE SYNTHESIS OF IMIDAZOLE-5-ONE

V. O. TOPUZYAN, V. M. GHAZOYAN, G. Sh. HOVHANNISYAN and A. A. HOVHANNISYAN

The Scientific and Technological Centre
of Organic and Pharmaceutical Chemistry NAS RA
26, Azatutyan Str., Yerevan, 0014, Armenia
E-mail: vtop@web.am

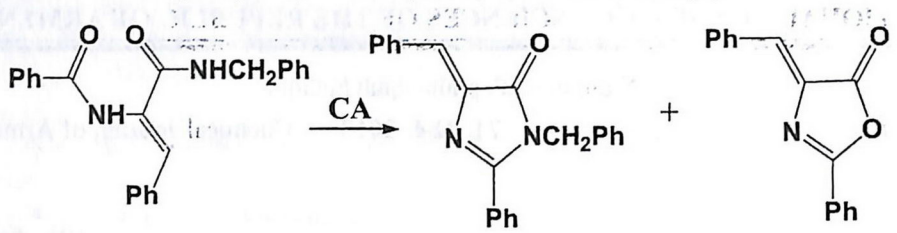
The effect of solvent, some additives and temperature on the dehydrating properties of dimethyldichlorosilane (DMDCS), trimethylchlorosilane (TMCS) and 1,1,1,3,3-hexamethyldi- silazane (HMDS) in the synthesis of 1-benzyl-2-phenyl-4-benzylidene-5-imidazolone from benzylamide N-benzoyl-α,β-dehydrophenylalanine was investigated. It was found that in the case of using DMDCS or TMHS as a reagent, the formation of a by-product - 2-phenyl-4-benzylidene-5-oxazolone was observed. Formation of the latter was not detected in the presence of triethylamine when TMCS was used as a silylating agent. The best results for the synthesis of imidazol-5-one (84%) were obtained with boiling the reaction mixture of benzylamide and HMDS in DMF for 15 *min*. Replacing DMF with dimethylacetamide, acetamide, formamide or pyridine, and lowering temperature of the reaction mixture reduces the yield of the target product. On the basis of the data obtained, it has been concluded that HMDS is an effective reagent for the synthesis of 1,2,4-tri-substituted imidazol-5-ones by dehydrating the amides of N-acyl-α,β-dehydroamino acids.

Table 1, references 13.

In the organic synthesis, silylating agents have found wide application. It is known that trimethylchlorosilane (TMCS) is used in the synthesis of ethers [1] and esters [2], and also promotes the reaction of Bedginelli [3]. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) has found application in the synthesis of imides of dicarboxylic acids [4] and phthalocyanines [5]. In recent years, TMCS [6], HMDS [7-10] and N, O-bistrimethylsilylacetamide (BTMSA) [11,12] have been used in the synthesis of 1,2-di- and 1,2,4-trisubstituted imidazol-5-ones.

The present work is devoted to the evaluation of dehydrating properties of some silylating agents in the synthesis of imidazol-5-ones. As the silylating agents (SA) TMCS, HMDS and dimethyldichlorosilane (DMDCS) were used. To assess the

dehydrating properties of some SA as a model, they were reacted with benzylamide of N-benzoyl-α,β-dehydrophenylalanine (**1**), dehydration of which resulted in the formation of 1-benzyl-2-phenyl-4-benzylidenimidazole-5-one (**2**).



1 **2** **3**

The influence of both the reaction conditions (reaction time, solvent, temperature, reagent ratio) and some additives (pyridine, triethylamine, N-methylmorpholine, imidazole) on the target product **2** was studied. The yield of product **2** was determined spectrophotometrically at 370-375 *nm* (maximum absorption of compound **2** in the UV spectrum). Amide **1** in this region did not show absorption. As the standard, we chose the absorption intensity at 275 nm of pure imidazolone **2** (Io). After the synthesis, the product, without purification, was studied for both the UV and IR spectra. To estimate the yield of compound **2**, the intensity (Ie) of the absorption spectrum of the reaction mixture at 370-375 *nm* was used. Calculations were carried out for compound **2** according to equation (1).

$$\% = \frac{\text{Iex } 100}{\text{Io}} \quad (1)$$

The IR spectrum was used to determine the presence in the reaction mixture of the parent substance **1** (3177-3271 cm^{-1}, NH-amide), the desired imidazole-4-one 2 (1710-1716 cm^{-1}, CO imidazolone) and the by-product 2-phenyl-4-benzylidene-5(4H)-oxazolone (3) (1791-1796 cm^{-1}, CO of oxazolone). The obtained results are given in the Table.

The results in the Table show that the use of DMDCS in DMF leads to the formation of a mixture, IR spectrum of which contains the characteristic absorption of both the starting material 1, the desired product 2 and the by-product 3 (table entries1-3). A similar picture is also observed in the case of using TMCS both separately (entries 4.5), and in the presence of pyridine (entries 8-10) or imidazole (entry 6) as additives. However, when triethylamine (entries11-12) or N-methyl-morpholine (entry 13) is used as an additive, by-product 3 is absent, but desired product 2 is obtained in low yields (11.8-25.5%). The reaction involving TMCS in DMF (entry 5), acetamide (entry 14) and dimethylacetamide (entry 15) proceeds with the formation of by-product 3. In formamide (entries 17,18), we do not register the formation of a by-product, however, desired product 2 is obtained in low yields (6.69-8.85%). When compound 1 is reacted with TMCS in dioxane or acetonitrile, the starting material is obtained unchanged back (entries 16,19).

Table

Influence of sililating agents (SA) - dimethyldichlorosilane (DMDCS), trimethylchlorosilane (TMCS), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), some additives (A) and the reaction conditions on the yield of imidazole-5-one 2, and IR spectrum of the obtained compounds

Entry №	SA	Relation **1**:SA	Solvent*	(A)**	Relation SA:A	Conditions	Time, *min*	Reaction product	Yield of prod.**2**, %	IR spectrum, ν, cm^{-1}
1	DMDCS	1:3	DMF	–		boiling	60	mixture **1,2,3**	–	1716 (C=O **2**) 1792 (C=O **3**) 3233 (NH **1**)
2	DMDCS	1:3	DMF	Py	1:1	boiling	60	mixture **1,2,3**	–	1714 (C=O **2**) 1794 (C=O **3**) 3245 (NH **1**)
3	DMDCS	1:3	DMF	NEt_3	1:1	boiling	60	mixture **1,2,3**	–	1715 (C=O **2**) 1794 (C=O **3**) 3232 (NH **1**)
4	TMCS	1:3	DMF	–	–	boiling	30	mixture **1,2,3**	–	1713 (C=O **2**) 1794 (C=O **3** 3221 (NH **1**)
5	TMCS	1:3	DMF	–	–	boiling	60	mixture **1,2,3**	–	1715 (C=O **2**) 1791 (C=O **3** 3225 (NH **1**)
6	TMCS	1:3	DMF	Im	1:1	boiling	60	mixture **1,2,3**	–	1710 (C=O **2**) 1796 (C=O **3**) 3235 (NH **1**)
7	TMCS	1:3	DMF	Py	3:1	boiling	60	mixture **1,2**	10.21	1716 (C=O **2**) 3255 (NH **1**)
8	TMCS	1:3	DMF	Py	1:1	boiling	60	mixture **1,2,3**	–	1712 (C=O **2**) 1794 (C=O **3**)

										3238 (NH **1**)
9	TMCS	1:3	DMF	Py	3:10	boiling	60	mixture **1,2,3**	–	1712 (C=O **2**) 1794 (C=O **3**) 3234 (NH **1**)
10	TMCS	1:3	DMF	Py	3:20	boiling	90	mixture **1,2,3**	–	1710 (C=O **2**) 1794 (C=O **2**) 3262 (NH **1**)
11	TMCS	1:3	DMF	NEt_3	1:1	boiling	60	mixture **1,2**	24.41	1716 (C=O **2**) 3215 (NH **1**)
12	TMCS	1:3	DMF	NEt_3	3:10	boiling	60	mixture **1,2**	25.49	1716 (C=O **2**) 3242 (NH **1**)
13	TMCS	1:3	DMF	NMM	1:1	boiling	60	mixture **1,2**	11.76	1715 (C=O2) 3231 (NH **1**)
14	TMCS	1:3	AA	–	–	120°C	60	mixture **1,2,3**	–	1715 (C=O2) 1796 (C=O **3**) 3258 (NH **1**)
15	TMCS	1:3	DMAA	–	–	150°C	60	mixture **1,2,3**	–	1716(C=O2) 1792 (C=O **3**) 3271 (NH **1**)
16	TMCS	1:3	AN	–	–	boiling	60	**1**	0	3177 (NH **1**)
17	TMCS	1:3	FA	–	–	150°C	30	mixture **1,2**	6.69	1714 (C=O **2**) 3242 (NH **1**)
18	TMCS	1:3	FA	–	–	150°C	60	mixture **1,2**	8.85	1714 (C=O **2**) 3237 (NH **1**)
19	TMCS	1:3	DO	–	–	boiling	60	**1**	0	3226 (NH **1**)
20	TMCS/HMDS 1:1	1:3	DMF	–	–	boiling	60	**1**	0	3222 (NH **1**)
21	HMDS	1:2	DMF	–	–	boiling	60	mixture	52.13	1711 (C=O **2**)

								1,2		3243 (NH **1**)
22	HMDS	1:3	DMF	–	–	boiling	10	mixture **1,2**	39.42	1711 (C=O **2**) 3223 (NH **1**)
23	HMDS	1:3	DMF	–	–	boiling	15	**2**	84.05	1716 (C=O **2**)
24	HMDS	1:3	DMF	–	–	boiling	20	**2**	75.25	1710 (C=O **2**)
25	HMDS	1:3	DMF	–	–	boiling	30	**2**	70.99	1716 (C=O **2**)
26	HMDS	1:3	DMF	–	–	boiling	60	**2**	67.88	1716 (C=O **2**)
27	HMDS	1:3	DMF	–	–	100°C	60	mixture **1,2**	9.26	1711 (C=O **2**) 3208 (NH **1**)
28	HMDS	1:3	DMF	–	–	120°C	60	mixture **1,2**	26.16	1713 (C=O-**2**) 3247 (NH **1**)
29	HMDS	1:7	–	–	–	100°C	60	**1**	0	3213 и 3285 (NH **1**)
30	HMDS	1:3	AN	–	–	boiling	60	**1**	0	3243 (NH **1**)
31	HMDS/ DMFA 1:2	1:3	AN	–	–	boiling	60	**1**	0	3211 (NH **1**)
32	HMDS	1:3	Py	–	–	boiling	60	mixture **1,2**	13.32	1716 (C=O **2**) 3218 (NH **1**)
33	HMDS	1:3	DO	–	–	boiling	60	**1**	0	3227 (NH **1**)
34	HMDS	1:3	FA	–	–	150°C	30	mixture **1,2**	10.07	1713 (C=O **2**) 3242 (NH **1**)
35	HMDS	1:3	FA	–	–	150°C	60	mixture **1,2**	12.78	1710 (C=O**2**) 3247 (NH **1**)
36	HMDS	1:3	DMAA	–	–	150°C	60	**1**	0	3266 (NH **1**)

*DMF – dimethylformamid, AA –acetamid, DMAA – dimethylacetamid, FA – formamide, AN – acetamide; DO – dioxin; ** Im – imidazole, Py – pyridine, NMM – N-methylmorpholine.

The results in the Table also show that dioxane or acetonitrile do not allow the reaction to proceed with HMDS (entries 30, 33), however, the reaction in dimethylformamide has good results after 15 *min* (entry 23). Moreover, in the IR spectrum of the obtained reaction product, in addition to absorption at 1716 cm-1, no other absorption characteristic of compounds 1 and 3 is observed. It should be noted that prolongation of the interaction time leads to a decrease in the yield of desired product 2 (entries 24-26). In this case tar formation occurs. When the reaction is carried out at relatively low temperatures (100 or 120°C, entries 27 and 28) no satisfactory results are observed. A similar result is also obtained when compound 1 is reacted with HMDS in the solvent-free conditions or in pyridine, acetonitrile, dioxane, acetamide, formamide or dimethylacetamide (entries 29-36). The use of a mixture of TMCS-HMDS in DMF does not result in the formation of desired product 2 (entry20).

Thus, from the investigated silylating agents for the synthesis of imidazol-5-one, HMDS is the best one, which in DMF comparatively quickly (15 *min*) leads to the formation of the desired product in high yield (84%). Also note that the proposed [11] BDSA cyclization of amides of N-formyl-α,β-dehydroamino acids in imidazol-5-ones is carried out in pyridine at 100°C for 12 *h* with a yield of 52-98%. Based on this, it can be concluded that HMDS exhibits high efficiency as a cyclocondensing agent for the synthesis of imidazol-5-ones from the corresponding amides of N-substituted α,β-dehydroamino acids.

Experimental Section

The IR spectra were recorded on a spectrometer in vaseline oil, the ^{1}H NMR spectra were measured on a Varian "Mercury-300" spectrometer in DMSO-d_6 using TMS as internal standard. The UV spectra were recorded on Thermo Electron Corporation "Helios Y" spectrometer. TLC was carried out on "Silica Gel" 60 F_{254} plates in the system benzene:methanol= 5:2, developer – iodine vapor. 4-Benzylidene-5(4H)-oxazolone was synthesized according to [13].

N-benzoyl-α,β-dehydrophenylalaninebenzylamide (1). To a solution of 2.5 *g* (10 mmol) of 2-phenyl-4-benzylidene-5(4H)-oxazolone in 25 *ml* of ethylacetate was added 1.18 *g* (1.2 *ml*, 11 *mmol*) of amine and allowed to stand at room temperature for 24 *h*. The formed precipitate was filtered off, washed with 25 *ml* of diethyl ether and air-dried. Recrystallized from 50% ethanol. Yield 85.71%, mp 178-180°C, R_f 0.48. IR spectrum, γ, cm^{-1}: 1639 (C=O-amide), 3265 (NH). NMR spectrum, ^{1}H NMR, δ, ppm, *Hg*: 4.45 (2H, d, J 6,1, CH_2), 7,16-7,38 (9H, m, Ar), 7.43-7,59 (5H, m, Ar), 8.02-8.08 (2H, m, Ar), 8.45 (1H, t, J 6.1 NHCH_2), 9.76 (1H, s, NH). UV spectrum, λ, nm (lg ε): 276 (1.098).

1-Benzyl-2-phenyl-4-benzylidene-5-imidazolone (2). To a solution of 0.5 *g* (1.4 *mmol*) of compound 1 in 5 *ml* of DMF was added 0.68 *g* (0.89 *ml*, 4.2 *mmol*) of 1,1,1,3,3,3-hexamethyl- disilazane and the reaction mixture was refluxed for 30 *min*. 45 *ml* of water was added, acidified to pH 6. The formed precipitate was filtered off,

washed with water and air-dried. The product was dissolved in 30 *ml* of benzene, 1.0 *g* of activated carbon was added, the mixture was refluxed for 30 *min*, cooled to room temperature and filtered. After removal of benzene on a rotary evaporator, the residue was 0.31 *g* (65.96%). Yield 65.96 %, mp 147-149, R_f 0.79. IR spectrum, γ, cm^{-1}: 1715 (C=O-cycle). ^{1}H NMR spectrum, δ, ppm: 4.95 (2H, s, CH_2), 7.09-7.14 (2H, m, Ar), 7.19 (1H, s, =CH), 7.21-7.31 (3H, m, Ar), 7.35-7.56 (6H, m, Ar), 7.67-7.72 (2H, m, Ar), 8.23-8.28 (2H, m, Ar). UV spectrum, λ, *nm* (lg ε): 248 (0.949), 295 (0.620), 371 (1.479).

Preparation of samples for UV research. To a solution of 0.5 *g* (1.4 *mmol*) of compound **1** in 5 *ml* of a solvent, 2.8-4.2 *mmol* of silylating reagent was added, and, if necessary, an appropriate additive (Table), and the mixture was boiled for 10 to 90 *min*. 45 *ml* of water was added and left at room temperature for 3 *h*. The precipitate formed was filtered off and thoroughly air dried to obtain a homogeneous mass. To 10 *mg* of the latter, 10 *ml* of ethanol was added, the resulting solution was diluted with ethanol 100 times, and the UV spectrum of the resulting solution was recorded.

ԻՄԻԴԱԶՈԼ-5-ՈՆՆԵՐԻ ՍԻՆԹԵԶՈՒՄ ՈՐՈՇ ՍԻԼԻԼԱՑՆՈՂ ԱԳԵՆՏՆԵՐԻ ԴԵՀԻԴՐԱՏԱՑՆՈՂ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ԳՆԱՀԱՏՈՒՄԸ

Վ. Օ. ԹՈՓՈՒԶՅԱՆ, Վ. Մ. ՂԱԶՈՅԱՆ,
Գ. Շ. ՀՈՎՀԱՆՆԻՍՅԱՆ և Ա. Ա. ՀՈՎՀԱՆՆԻՍՅԱՆ

Ուսումնասիրված է լուծիչի, ջերմաստիճանի և մի քանի հավելանյութերի ազդեցությունը դիմեթիլդիքլորսիլանի (ԴՄԴՔՍ), տրիմեթիլքլորսիլանի (ՏՄՔՍ) և 1,1,1,3,3,3-հեքսամեթիլդիսիլազանի դեհիդրատացնող հատկությունների վրա N-բենզոիլ-α,β-դեհիդրոֆենիլալանինից 1-բենզիլ-2-ֆենիլ-4-բենզիլիդեն-5-իմիդազոլոնի ստացման ռեակցիայում: Պարզված է, որ ԴՄԴՔՍ և ՏՄՔՍ օգտագործման դեպքում, բացի նպատակային իմիդազոլոնից, գոյանում է նաև կողմնակի արգասիք՝ 2-ֆենիլ-4-բենզիլիդեն-5-օքսազոլոն: Վերջինիս առաջացումը չի նկատվում տրիէթիլամինի ներկայությամբ ՏՄՔՍ որպես դեհիդրատացնող ագենտ կիրառման դեպքում: Իմիդազոլ-5-ոնի ստացման լավագույն արդյունքները (84%) ստացվում են ՀՄԴՍ և բենզիլամիդի խառնուրդը ԴՄՖԱ 15 րոպե եռացնելու դեպքում: ԴՄՖԱ-ի փոխարինումը դիմեթիլացետամիդով, ացետամիդով, ֆորմամիդով կամ պիրիդինով հանգեցնում է նպատակային միացության ելքի նվազմանը: Ստացված արդյունքների հիման վրա արված է եզրակացություն, որ ՀՄԴՍ հանդիսանում է արդյունավետ ռեագենտ N-ացիլ-α,β-դեհիդրոամինաթթուների ամիդներից 1,2,4-եռատեղակալված իմիդազոլ-5-ոների սինթեզի համար:

ОЦЕНКА ДЕГИДРАТИРУЮЩИХ СВОЙСТВ НЕКОТОРЫХ СИЛИЛИРУЮЩИХ АГЕНТОВ ПРИ СИНТЕЗЕ ИМИДАЗОЛ-5-ОНА

В. О. ТОПУЗЯН, В. М. КАЗОЯН, Г. Ш. ОГАННИСЯН и А. А. ОГАНЕСЯН

Исследовано влияние растворителя, некоторых добавок и температуры на дегидратирующие свойства диметилдихлорсилана (ДМДХС), триметилхлорсилана (ТМХС) и 1,1,1,3,3,3-гекса-метилдисилазана (ГМДС) при синтезе 1-бензил-2-фенил-4-бензилиден-5-имидазолона из бензиламида N-бензоил-α,β-дегидрофенилаланина. Установлено, что в случае применения в качестве реагента ДМДХС или ТМХС наблюдается образование побочного продукта – 2-фенил-4-бензилиден-5-оксазолона. Образование последнего не обнаружено в присутствии триэтиламина

при применении в качестве силилирующего агента ТМХС. Наилучшие результаты синтеза имидазол-5-она (84%) получены при кипячении реакционной смеси бензиламида, ГМДС в ДМФА в течение 15 *мин*. Замена ДМФАна диметилацетамид, ацетамид, формамид или пиридин, а также снижениетемпературы реакционной смеси приводит к уменьшению выхода целевого продукта. На основании полученных данных сделано заключение, что ГМДС является эффективным реагентом для синтеза 1,2,4-тризамещенных имидазол-5-онов дегидратацией амидов N-ацил-α,β-дегидроаминокислот.

REFERENCES

[1] *Izumi M., Fukase K., Kusumoto Sh.* // Biosci.Biotechnol.Biochem., 2002, v.66, №1, p.211.

[2] *Jordi E.J., Francisca V.T., Ramon C.G.* // RevistaTumbagu, 2007, v.2, p.85.

[3] *Ryabukhin S.V., Plaskon A.S., Ostapchuk E.M., Volochnyuk D.M.* // Synthesis, 2007, №3, p.417.

[4] *Reddy P.Y., Kondo S., Toru T., Ueno Y.* // J. Org. Chem., 1997, v.62, p. 2652.

[5] *Uchida H., Yoshiyama H., Reddy P.Y., Nakamura Sh., Toru T.* // Bull.Chem.Soc.Jpn., 2004, v.77, p.1401.

[6] *Топузян В.О., Оганесян А.А., Паносян Г.А.* // ЖОрХ, 2004, т.40, №11, с.1692.

[7] *Топузян В.О., Арутюнян Л.Г., Оганесян А.А.* // ЖОрХ, 2007, т.43, №6, с.870.

[8] *Топузян В.О., Арутюнян Л.Г., Оганесян А.А., Паносян Г.А.* // ЖОрХ, 2007, т.43, №6, с.936

[9] *Топузян В.О., Арутюнян Л.Г., Оганесян А.А., Паносян Г.А.* // ЖОрХ, 2008, т.44, №3, с.474.

[10] *Тосунян С.Р.* Хим.ж.Армении, 2013, т.66, №2, с.316.

[11] *Muselli M., Colombeau L., Hedouin J., Hoarau C., Bishoff L.* // Synlett, 2016, v.27, p. 2819.

[12] *Muselli M., Beudequin C, Perrio C., Hoarau C., Bishoff L.* // Chem. Eur. J., 2016, v.22, p.5520.

[13] *Wang Y., Shi D., Lu Z., Dai G.* // Synthet.commun., 2000, v.30, №4, p.707.