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 **72, №4, 2019** Chemical Journal of Armenia

ALKYLATION OF IMIDAZOLE WITH DICHLOROETHANE AND DEHYDROCHLORINATION OF THE IN-SITU OBTAINED 1-(2'-CHLOROETHYL)IMIDAZOLE TO 1-VINYLIMIDAZOLE IN AN AQUEOUS ALKALINE MEDIUM IN THE N-METHYLMORPHOLINE N-OXIDE SYSTEM USING PHASE TRANSFER CATALYST

A. H. HASRATYAN[2], A. A. SUQOYAN[2], G. G. DANAGULYAN[1,2] and H. S. ATTARYAN[2]

[1]Russian-Armenian (Slavonic) University
123, H. Emin Str., Yerevan, 0051, Armenia
E-mail: hovelenatt@mail.ru
[2]The Scientific Technological Center of Organic and
Pharmaceutical Chemistry NAS RA
26, Azatutyan Str., Yerevan, 0014, Armenia
E-mail: ani_hasratyan@mail.ru

In this article, the possibility of applying phase transfer catalysis (PTC) in the N-methylmorpholine-N-oxide-water system for the alkylation of imidazole with dichloroethane was considered. It has been shown that the alkylation of imidazole with dichloroethane in the aforementioned system is accompanied by dehydrochlorination of the in situ obtained 1-(2'-chloroethyl)imidazole, which allows the synthesis of 1-vinylimidazole without the use of explosive acetylene.

References 21.

N-vinylazoles are an important class of azole derivatives that can form radical polymerization and copolymerization products [1-7]. Many vinylazole-based polymeric compounds exhibit biological activity and serve as effective drugs [8-10].

In [11-12] articles, we showed that the alkylation reaction of azoles in the NMO/H_2O system in comparison to various phase transfer catalysts was not inferior in reaction yields during phase transfer catalysis (PTC).

In this communication, the possibility of using phase transfer catalysis (PTC) in the N-methylmorpholine-N-oxide-water (NMO) system was considered.

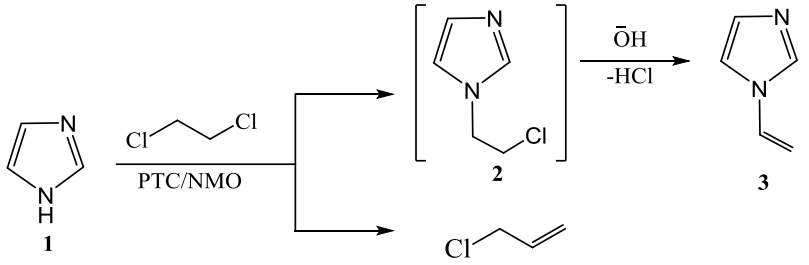
Further, our studies on the alkylation of imidazole (**1**) with dichloroethane using phase transfer catalysts (quaternary ammonium salts) in an aqueous solution of N-methylmorpholine-N-oxide (NMO/H_2O) were carried out.

According to published data, there are many examples of N-alkylation of imidazole (**1**) under PTC conditions [13-17], but there is no alkylation of imidazole with dichloroethane.

The need for development was dictated by the fact that 1-(2-chloroethyl)imidazole (**2**) is simultaneously an intermediate product in the synthesis of an important class of 1-vinylimidazole, on the other hand, 1-vinylimidazole and its derivatives are still obtained under acetylene pressure at a temperature of 130 °C and higher [18].

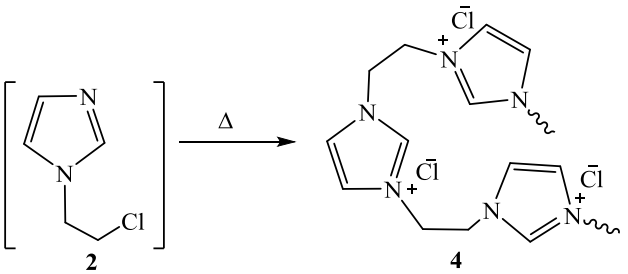
During the alkylation reaction of imidazole (**1**) with dichloroethane (^{1}H NMR spectroscopic control) in the PTC/NMO system, it has been found that in the absence of a base the alkylation reaction does not proceed, and in the presence of sodium hydroxide, alkylation is also accompanied by elimination of dichloroethane according to Scheme 1.

Scheme 1



It has been found that the basicity is the determining factor for the isolation of 1-(2'-chloroethyl)imidazole (**2**) from the reaction medium. The basicity of imidazole (**1**) upon proton addition is $_pk^a$=6.95, while the basicity value of pyrazole or 1,2,4-triazole is $_pk^a$=2.2-2.5 [19]. Therefore, the monoalkylation product of imidazole (**1**), in comparison with pyrazole or 1,2,4-triazole [20-21], undergoes intermolecular quaternization upon distillation with the formation of polysalt **4** according to Scheme 2.

Scheme 2



The presence of 1-(2'-chloroethyl)imidazole (**2**) in the reaction medium was proved by ^{1}H NMR spectroscopy. With an equimolar ratio of imidazole: sodium hydroxide and a five-fold excess of dichloroethane (DCE), the yield of compound **2** after three hours is 1.2 *g* (9.2%). The low yield of 1-(2'-chloroethyl)imidazole (**2**) is due to the fact that the relatively high basicity of

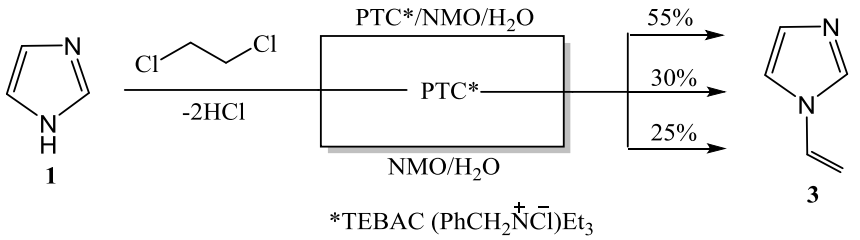
imidazole ($_pk^a$ 6.95) makes it difficult to deprotonate it under the influence of sodium hydroxide and the base is used to eliminate dichloroethane.

When a second portion of sodium hydroxide is added, the alkylation continues, at the same time the alkylated product is in-situ dehydrochlorinated to 1-vinylpyrazole (**3**), the elimination of dichloroethane continues parallel, therefore, both dichloroethane and sodium hydroxide must be taken in excess.

It has been experimentally found that the molar ratio of reagents – imidazole:NaOH:DCE is equal to 0.1:1.2:1.5, which within 7-8 hours provides 50-55% yield of 1-vinylimidazole (**3**) in the PTC/NMO/H_2O system.

Alkylation of imidazole (**1**) with dichloroethane and the dehydrochlorination of the in-situ obtained 1-(2'-chloroethyl)imidazole in an aqueous alkaline medium in the presence of NMO and PTC has also been studied (Scheme 3).

Scheme 3



Thus, it has been shown that PTC can be successfully used compatible with an aqueous solution of NMO during alkylation reactions.

The study was carried out at the Russian-Armenian University at the expense of the funds allocated under the subsidy of the Ministry of Education and Science of Russia to finance research activities of the RAU. The research was carried out with the financial support of the State Committee for Science of the Ministry of Education and Science of the Republic of Armenia within the framework of the scientific project №18T-2E151.

Experimental Section

IR spectra are recorded on a "Termo Nicoletion Nexus" spectrometer in vaseline oil. NMR spectra of ^1H and ^{13}C of the synthesized compounds were recorded on a Varian "Mercury-300 VX" spectrometer (300 and 75 MHz, respectively) at a temperature of 300 K in a solution of DMSO-d6-CCl_4 1:3 (internal standard-TMS). Elemental analysis is performed on a "Eurovector EA-3000" device.

1-(2'-Chlorethyl)imidazole (2). A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 50 *g* (0.5 *mol*) of dichloroethane, 4 *g* (0.1 *mol*) of sodium hydroxide, 1 *g* (TEBAC) in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 3 hours. After cooling, it was extracted with chloroform. After removal of chloroform, 1.2 *g* (9.2%) of 1-(2'-chloroethyl)imidazole (**2**) was

obtained, which was proved by ^{1}H NMR spectroscopy. NMR ^{1}H δ, ppm, *J* (Hz): 3.85 t (2H, CH_2, *J* = 6.2), 4.39 t (2H, CH_2, *J* = 6.2), 7.12 br. s (1H, 4-H), 7.39 t (1H, 5-H, *J* = 1.5), 7.78 br. s (1H, 2-H). Upon distillation, compound (**2**) was quaternized to polysalt (**4**) with a m.p. 144-149 °C, [ή]=0.02 dl/g. IR spectrum, ν, cm^{-1}: 1510 (ring), 2000 (salt effect).

1-Vinylimidazole (3). A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide, 1 *g* (TEBAC) in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 3 hours. Then, a solution of 40 *g* (1.0 *mol*) of sodium hydroxide in 100 *ml* of water is added dropwise over 2 *hours* and stirring is continued for 5 hours. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform, the organic layer was dried over calcium chloride. After removal of chloroform, the residue was distilled off under reduced pressure. The yield of 1-vinylimidazole (**3**) 5.2 *g* (55%), b.p. 71°C / 2 mm Hg, n_D^{20} 1.5300, d_4^{20} 1.039. IR spectrum, ν, cm^{-1}: 1510 (ring), 1650 (C=C). NMR ^{1}H δ, ppm, *J* (Hz): 5.06 dd (1H, $=CH_2$, *J* = 8.9 и 1.7), 5.50 dd (1H, $=CH_2$, *J* =15.8), 7.12 dd (1H, =CH, *J* = 15.8 и 8.9), 7.12 br. s (1H), 7.48 br. s (1H) и 7.91 br. s (1H, protons of the cycle). ^{13}C: 101.8 ($=CH_2$), 116.1 (C=H), 127.8 (N-CH), 128.7 (N=CH), 136.3 (NCHN). Found, %: C 63.78; H 6.04; N 30.13. $C_5H_6N_2$. Calculated, %: C, 51.79; H, 6.47; N, 30.21.

Synthesis of 1-vinylimidazole (3) under PTC conditions. A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide, 1 *g* (TEBAC) at 70-80°C was stirred vigorously for 2 hours. Then, a solution of 40 *g* (1.0 *mo*l) of sodium hydroxide in 100 *ml* of water was added dropwise over 2 hours and stirring is continued for 5 hours. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform. After removal of chloroform, the residue was distilled off under reduced pressure. Yield of 1-vinylimidazole (**3**) 2.8 *g* (30%), b.p. 68 °C / 1 mm Hg, n_D^{20} 1.5300.

Synthesis of 1-vinylimidazole (3) in the NMO/H_2O system. A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 2 *hours*. Then, a solution of 40 *g* (1.0 *mol*) of sodium hydroxide in 100 *ml* of water is added dropwise over 2 *hours* and stirring is continued for 5 *hours*. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform. After removal of chloroform, the residue was distilled off under reduced pressure. The yield of 1-vinylimidazole (**3**) 2.3 *g* (25%), b.p. 71°C / 3 *mm* Hg, n_D^{20} 1.5300.

ԻՄԻԴԱԶՈԼԻ ԱԼԿԻԼԱՑՈՒՄԸ ԴԻՔԼՈՐԷԹԱՆՈՎ ՋՐԱԽԻՄՆԱՅԻՆ ՄԻՋԱՎԱՅՐՈՒՄ N-ՄԵԹԻԼՄՈՐՖՈԼԻՆ N-ՕՔԻԴԻ ՀԱՄԱԿԱՐԳՈՒՄ ՄԻՋՓԱԶ ԿԱՏԱԼԻԶԱՏՈՐԻ ՕԳՏԱԳՈՐԾՄԱՄԲ ԵՎ IN-SITU ՊԱՅՄԱՆՆԵՐՈՒՄ ԱՌԱՋԱՑԱԾ 1-(2'-ՔԼՈՐԷԹԻԼ)ԻՄԻԴԱԶՈԼԻ ԴԵՀԻԴՐՈՔԼՈՐԱՑՈՒՄԸ 1-ՎԻՆԻԼԻՄԻԴԱԶՈԼԻ

Ա. Կ. ՀԱՍՐԱԹՅԱՆ[2], Ա. Ա. ՍՈՒՔՈՅԱՆ[2],
Գ. Գ. ԴԱՆԱԳՈՒԼՅԱՆ[1] և Հ. Ս. ԱԹԹԱՐՅԱՆ[1]

Ներկայացված աշխատանքում իրականացվել է իմիդազոլը ալկիլացումը դիքլորէթանով ջրահիմնային միջավայրում միջֆազ կատալիզի օգտագործմամբ N-մեթիլմորֆոլին N-օքիդ-ջուր համակարգում: Ցույց է տրվել, որ նշված համակարգում իմիդազոլի ալկիլացումը դիքլորէթանով ուղեկցվում է in situ պայմաններում ստացված 1-(2'-քլորէթիլ)իմիդազոլի դեհիդրոքլորացման՝ 1-վինիլիմիդազոլի առաջացմամբ, ինչը թույլ է տալիս վերջինիս սինթեզը առանց պայթունավտանգ ացետիլենի օգտագործման:

АЛКИЛИРОВАНИЕ ИМИДАЗОЛА ДИХЛОРЭТАНОМ И ДЕГИДРОХЛОРИРОВАНИЕ IN-SITU ПОЛУЧЕННОГО 1-(2'-ХЛОРЭТИЛ)ИМИДАЗОЛА ДО 1-ВИНИЛИМИДАЗОЛА В ВОДНО-ЩЕЛОЧНОЙ СРЕДЕ В СИСТЕМЕ N-МЕТИЛМОРФОЛИН N-ОКСИДА С ИСПОЛЬЗОВАНИЕМ КАТАЛИЗАТОРА МЕЖФАЗНОГО ПЕРЕНОСА

А. Г. АСРАТЯН[2], А. А. СУКОЯН[2], Г. Г. ДАНАГУЛЯН[1,2] и О. С. АТТАРЯН[2]

[1]Российско-Армянский (Славянский) университет
Армения, 0051, Ереван, ул. Овсепа Эмина 123
E-mail: hovelenatt@mail.ru
[2]Научно-технологический центр органической и фармацевтической химии НАН РА
Армения, Ереван, 0014, пр. Азатутян, 26
E-mail: ani_hasratyan@mail.ru

В настоящей работе рассматривается возможность применения межфазного катализа в системе N-метилморфолин-N-оксид-вода при алкилировании имидазола дихлорэтаном. Показано, что алкилирование имидазола дихлорэтаном в вышеуказанной системе сопровождается дегидрохлорированием in situ полученного 1-(2'-хлорэтил)имидазола, что позволяет провести синтез 1-винилимидазола без использования взрывоопасного ацетилена.

REFERENCES

[1] *Татарова Л.А., А.А. Берлин, Разводовский Е.Ф., Ермакова Т.Г., Лопырев В.А., Кедрина Н.Ф., Еникалопов Н.С.* // Высокомолек. соед., 1985, А 24, №10, с. 2205.
[2] *Гамкова Л.А., Морозова И.С., Ермакова Т.Г., Лопырев В.А., Кедрина Н.Ф., Еникалопян Н.С.* // Высокомолек. соед., 1983, А 25, №1, с. 14.
[3] *Даниловцева Е.Н., Анненков В.В., Михалев А.И., Трофимов Б.А.* // Высокомолек. соед., 2004, А 46, №2, с. 241.
[4] *Анненков В.В., Мазяр Н.Л., Круглова В.А.* // Высокомолек. соед., 2001, А 36, с. 862.
[5] *Скушникова А.И., Досинина Е.С., Скворцова Г.Г.* // Высокомолек. соед., 1979, Б 21, с. 8.

[6] *Хримян А.П., Карапетян А.В., Церунян В.В., Дарбинян Э.Г., Баданян Ш.О.* // Арм. хим. ж., 1986, т. 37, №5, с. 331.
[7] *Lyoo W.S., Choi J.H., Han S.S., Yoon W.S., Park M.S., Ji B.C., Cho J.* // J. Appl. Polym. Sci., 2000, v. 78, p. 438. doi.org/10.1002/1097-4628(20001010)78:2<438::AID-APP240>3.0.CO;2-S.
[8] *Хачатрян С.Ф., Аттарян О.С., Мацоян М.С., Оганесян А.С.* // Международная академия наук экологии и безопасности жизнедеятельности, Вестник, Санкт-Петербург, 2006, т. 11, №8, с. 263.
[9] *Куно К., Хидео Т., Мотокум М.. Кодж С.* Полимерые препараты, содержащие винилимидазольные группы для снижения уровня холестерина. Пат. США N 441, 2011, опубл. РЖХ N12095 II1984.
[10] *Zhang Y., Chen X., Lan J., You J., Chen L.* // Chem. Biol. Drug. Des., 2009, v. 74, p. 282. doi.org/10.1111/j.1747-0285.2009.00858.x.
[11] *Закарян Г.Б., Айоцян С.С., Айвазян А.Г., Тамазян Р.А., Паносян С.А., Данагулян Г.Г., Аттарян О.С.* // ХГС, 2016, т. 52, с. 253. doi.org/10.1007/ s10593-016-1870-2.
[12] *Асратян А.Г., Алексанян А.Г., Хачатрян А.Н., Закарян Г.Б., Айоцян С.С., Данагулян Г.Г., Аттарян О.С.* // ХГС, 2018, т. 54 (7), с. 751. doi.org/10.1007/s10593-018-2342-7.
[13] *Dou H.J.M., Metzger J.* // Bull. Soc. Chim. France, 1976, №11, p. 1861.
[14] *Pilarski B.* // Liebigs. Ann. Chem. 1983, v. 16, p. 1078, doi.org/10.1002/jlac.198319830619
[15] *Claranunt R.M., Elguero J., Garceran C.* // Heterocycles, 1985, v. 23, №11, p. 2895. doi.org/10.3987/R-1985-11-2895.
[16] *Golons H., Bergerat J.,Combet-Farnoux C., Miocque M., Decods G., Bram G.* // J. Soc. Chem. Commun. 1985, №23, p. 1730. doi.org/10.1039/C39850001730.
[17] *Claranunt R.M., Elguero J., Meco T.* // J. Heterocycl. Chem., 1983, v. 20, №5, p. 1245. doi.org/10.1002/jhet.5570200519.
[18] *Шостаковский М.Ф., Скворцова Г.Г., Глазкова Н.П., Дошнина Е.С.* // ХГС, 1962, №6, с. 1070.
[19] *Иванский В.И.* // ХГС, М., Высшая школа. 1978, с. 48.
[20] *Аттарян О.С., Мацоян С.Г., Мартиросян* // ХГС, 2005, т. 41, №4, с. 533.
[21] *Аттарян О.С., Асратян Г.В., Элиарян Г.А., Дарбинян Э.Г., Мацоян С.Г.* // Арм. хим. ж., 1986, т. 39, №10, с. 630.