UDC 66.061.35+547-38

DEEP EUTECTIC SOLVENT (RELINE) AS CATALYTIC SYSTEM IN SYNTHESIS OF SCHIFF BASES DERIVED FROM GLUCOSE AND DIFFERENT AMINES

Zaynab M. Mahmood[1], Shakir M. Saied[2], Mohanad Y. Saleh[3,*]

[1]Ministry of Education, Nineveh Educational Directorate
[2]Department of Pharmacy, Al-Noor University College, Mosul, Iraq
[3]Department of Chemistry, College of Education for pure Science, Mosul University, Mosul, Iraq
e-mail: albdranyzynb@gmail.com; shakir.mahmood@alnoor.edu.iq;*mohanadalallaf@uomosul.edu.iq

Received 17.01.2024
Accepted 28.03.2024

Abstract: *In this work, seven new Schiff bases were obtained in two ways. In method (A), an equimolecular aqueous solution of glucose and an alcoholic solution of amine were refluxed for three hours, and in method (B), a deep eutectic solvent (Reline), prepared from one mole of choline chloride and two moles of urea,was used as catalyst. The reaction yield percentage in the traditional method (A) was found to be 60-79%, and in the catalytic method (Method B) using a deep eutectic solvent (Reline) yield percentage was 88-95%. The deep eutectic solvent catalytic system (Reline) is an environmentally friendly solution with the triple benefit of increased percentage yield, elimination of solvent, and faster reaction time by reducing reflux time by up to three times (i.e., just one hour).*
Keywords: *Glucose amine Schiff base, deep eutectic solvents, azomethane, α and β glucose amines.*
DOI: 10.32737/2221-8688-2024-3-281-289

Introduction

Schiff bases, which are also known as imines are important organic compounds of the azomethane functional group produced from the condensation of carbonyl compounds (glucose molecule in this work) and primary amines as shown in Fig.1 [1].

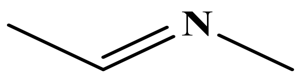

Fig. 1. Azomethane.

Schiff bases establish a significant class of organic products due to their excellent pharmaceutical characteristics [2]. Their broad-spectrum activities such as anti-infective agents arise from there, antifungal, antibacterial and even antineoplastic activity. These activities due to associated with their functional toxophoric group azomethane (C = N) [3].

Aliphatic and aromatic Schiff bases derived from glucose or other monosaccharides and primary amines has been reviewed, and the glucosyl amines products were primary α and β glucose amines which converted into Syn and Anti imino structures (Fig. 2) [4].

Deep eutectic ionic liquid (Reline), the ambient temperature molten salt [5], has attracted concentrated focus in most organic synthesis of this laboratory in the last two years [6] owing to its amazing properties such as very low vapor pressure, high thermal stability, and ionic conductivity. In addition to all these it has been used as an alternative solvent in organic synthesis [7], and it's a very simple synthesis approach from heating two moles of urea and one mole of choline chloride in an open test tube [8].

Deep eutectic solvents were employed in the synthesis of Schiff bases using choline chloride: malonic acid (1:1) based deep eutectic solvent [9].

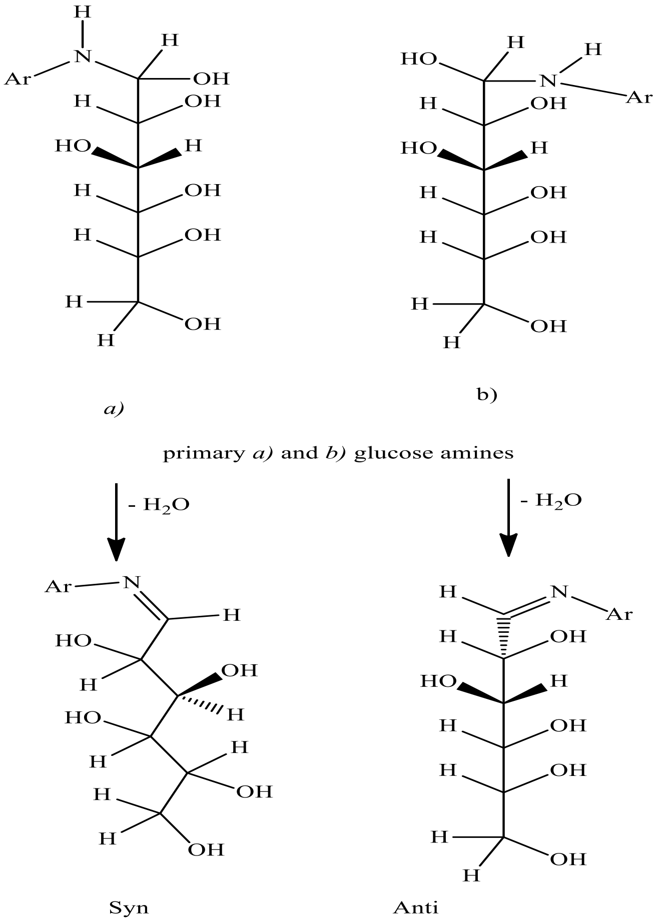

Fig. 2. Syn and Anti imino structures

The protocol for the synthesis of Schiff bases by the reaction of aldehydes with amines using the (Reline) deep eutectic solvent prepared from urea and choline chloride with good to high yields was very rare and modern, it started less than seven years ago only [10].

It is clear from the above literatures that the deep eutectic solvents (DESs) are hopeful maintainable substitutes to old-style solvents and are mostly composed of two harmless and low-cost eutectic mixture connected with a hydrogen bonds to produce a much lower boiling point than that of each mixture components, i.e. the choline chloride and urea [11], in addition to their thermal stability, little toxicity and ease of recyclability [12, 13].

Contributed to all this new knowledge and for the very importance of the use of a deep eutectic solvent (Reline) as a green catalyst of solventless and high yield percentage and as the continuation of our interest in using Reline catalyst, this new proposed objective was reported herein to improve the synthesis of novel Schiff bases derived from glucose sugar and appropriate amines.

Experimental part

Reagents or solvents were procured from a commercial source and used directly. Moreover, DES (Reline) was prepared. The IR spectra were recorded using a Bruker Alph FTIR Germany spectrophotometer using the KBr, and expressed in wave number ʋ (cm^{-1}). Then, ^{1}HNMR spectra of the synthesized compounds were recorded on a spectrophotometer of Bruker-Avance II 400 (400 MHz), using DMSO-d^6 solvent and TMS as an internal stander.

Synthesis of deep eutectic solvent (Reline) [13]: A mixture of choline chloride (0.1 mole) and urea (0.2 mole) was mixed manually using glass rode during heating at 100-120 °C until a clear solution began to form.

Then, the deep eutectic solvent (Reline) with the freezing point of the product was 12 ^{o}C was cooled and used without any purification.

Synthesis of glucose Schiff bases (1-7):

Conventional procedure, (Method A) [14]**:** Equimolecular mixture of aqueous solution of glucose (1.8gm, 10 mmole), glacial acetic acid (0.3 ml) and ethanol solution of appropriate amine was stirred under reflux for 3h the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water then dried and crystallized from ethanol.

Physical properties, percentage yield and spectral data are listed in Table 1.

Table 1. Physical data of the novel Schiff bases.

Compd no.	R	Yield, %; method		Colour	m.p., ^{o}C
		A	B		
1	4-nitrophenyl	76	90	yellow	45-47
2	2-nitrophenyl	60	92	yellow	142-44
3	2,4-nitrophenyl	60	95	bright brown	171-73
4	6-methylpyridenyl	67	89	bright white	138-40
5	2-methylbenzo[d]thiazolyl	69	88	light brown	119-20
6	benzo[d]thiazol-2-ylcarbamyl	77	92	milky white	88-92
7	2-phenyl-1,2-dihydro-3H-pyrazol-3-one-4yl-	79	92	light yellow	145-47

Catalytic procedure (Method B), Using deep eutectic solvent (Reline) [2]:

The equimolecular mixture of the aqueous solution of glucose (gm, 10 mmole) and appropriate amine with (1mmole) of DES (Reline) were stirred under reflux until the end of the reaction, which was checked by thin-layer chromatography (TLC). The crude product that was formed with addition of water was washed with ethanol to yield pure Schiff bases. Percentage yields are listed in Table 1. Note that all these Schiff-bases products by Method (B) were obtained had the exact specifications and spectrum measurements as those produced in Method (A). In addition, the purity of all products output for both methods (A and B) were equal melting points and mixed melting points.

Results and discussion

Frequently, glucose amine Schiff bases are formed by the reaction of amine with glucose in its reduction form, usually with the addition of catalysts such as acetic acid and solvent for example ethanol. In this article, seven Schiff bases were synthesized as anticipated potential bioactive agents via the route outline in the following Fig.3 [15].

To obtain the target Schiff bases, two routes were followed: In method (A), the conventional procedure for the synthesis of imines which are described in the literature involves the condensation of the reducing glucose (as aldehyde) with primary amines using acetic acid catalyst and ethanol as solvent. The amine here is a nucleophilic reagent that irreversibly attacks the electrophilic carbonyl carbon with the forming of an imine group via tetrahedral mechanism with the elimination of water [16].

In the suggested mechanism, it is important to change the reaction medium to an acidic using acetic acid catalyst which protonates the carbonyl oxygen and enhances the susceptibility of the carbonyl carbon to the nucleophilic attack of amine nitrogen and formation of the tetrahedral intermediate which eliminates the catalytic proton and a molecule of water to afford the imine group, as shown in Fig.4 [17].

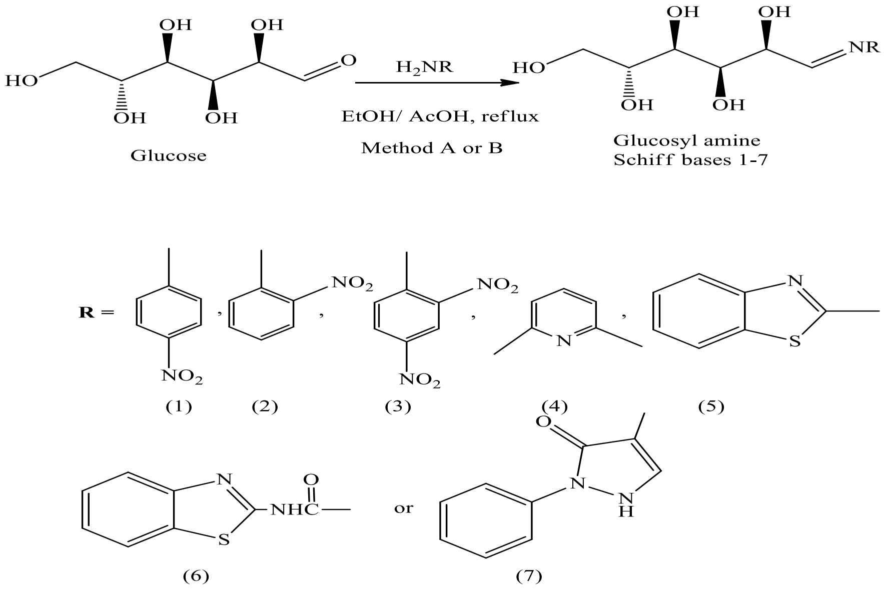

Fig. 3. Synthetic route of Glucosyl amine Schiff bases 1-7

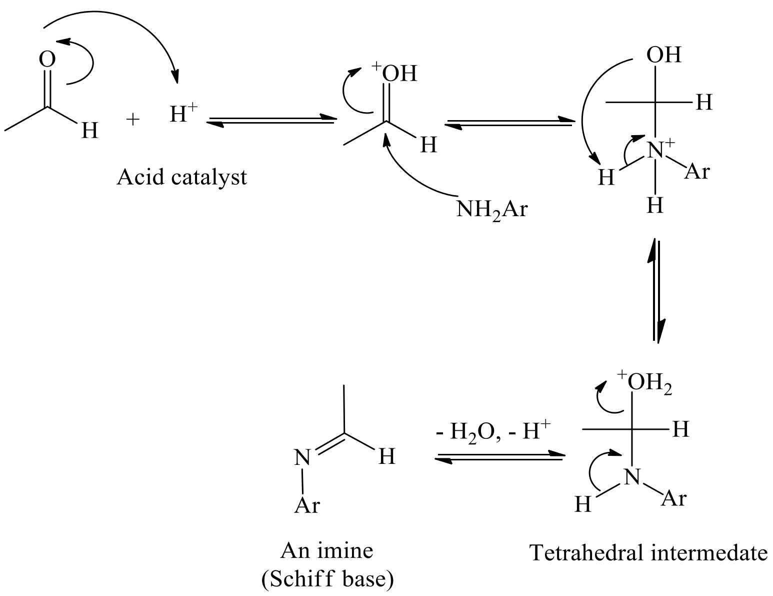

Fig.4. The tetrahedral mechanism of Imine (Schiff base) formation.

The yield percentages of Schiff base which were synthesized by the traditional methods (conventional procedure), (Method A) were 60-79% as shown in Table 1, which were enhanced to 88-95% by using the green catalyst deep eutectic solvent (Reline) which was prepared by the reaction of quaternary ammonium salt choline chloride and urea is atom efficient since all the atoms present in the starting materials are incorporated in the products [18].

Deep eutectic solvent (Reline) was initially used as a green solvent due to their exclusive physical and chemical properties, some of our new research marched far beyond this limit and verified their amazing role in accelerating the reactions as catalysts, and exhibited a significant increase in the yield percentages [19].

Reline, was prepared according to the equation in Fig.5. The mechanism of Deep eutectic solution (Reline) was shown in Fig. 6 [20].

This Deep eutectic solution (Reline), was a crucial solvent because it not only permits a good interaction with amine and glucose in the reaction mixture but also fixes the choice of work-up procedures and disposal strategies [21, 22].

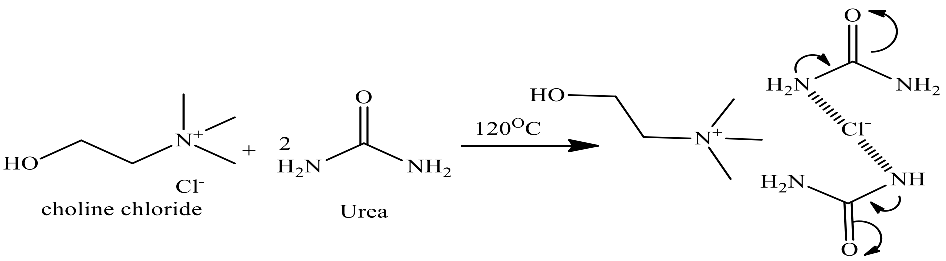

Fig. 5. Preparation of deep eutectic solvent (Reline).

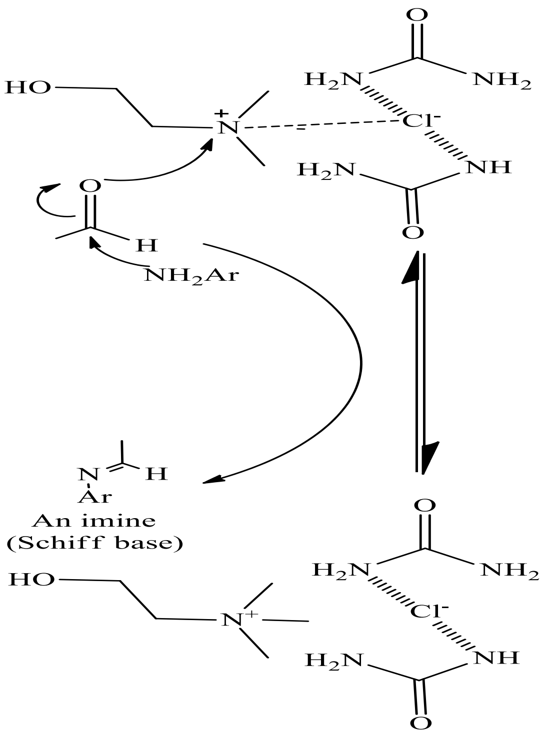

Fig. 6. Mechanism of Reline catalyst the Schiff base formation.

Also, a large amount of glucose can dissolve in a Deep eutectic solution (Reline), and similarly can dilute released water, thus limiting the side rehydration [23-25].

The chemical structures of these seven novel Schiff bases were conferred by FT-IR and ^{1}HNMR spectroscopy which were listed in Table 2 [26-29].

Table 2. The FT-IR and ^{1}HNMR spectroscopy of the novel Schiff bases

Compound No.	^{1}HNMR, ppm		IR, KBr, cm $^{-1}$
	Glucose moiety protons	C=N methine proton	The OH of glucose moiety
1	3.166 - 3.566	7.834-7.903	3395-3420
2	3.166 - 3.566	7.834-7.903	3390-3420
3	3.166 - 3.566	7.834-7.903	3387-3413
4	3.166 - 3.566	7.834-7.903	3388-3418
5	3.166 - 3.566	7.834-7.903	3389-3418
6	3.166 - 3.566	7.834-7.903	3395-3416
7	3.166 - 3.566	7.834-7.903	3393-3418

The FT-IR spectroscopic of these seven new Schiff bases exhibited the presence of characteristic absorption bands corresponding to the OH of glucose moiety in the region 3395-3420 cm^{-1}. This glucose moiety protons at [1]H-NMR spectra showed the signals at 3.166 - 3.566 ppm, and the C=N azomethane proton as a doublet in the range 7.834-7.903 ppm [26-29]. The IR (KBr, cm^{-1}) of Schiff base (1) as representative for these serious was shown in Fig. 7.

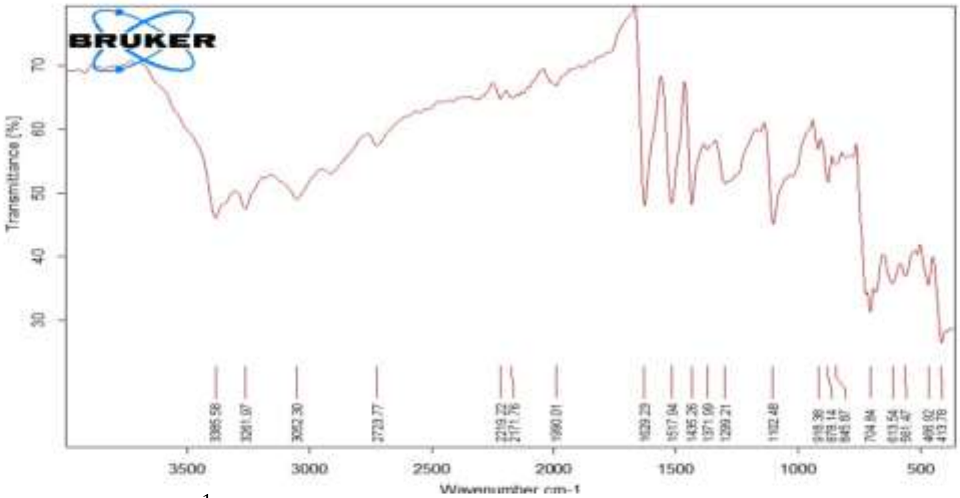

Fig. 7. The [1]HNMR of Schiff base (6) as representative of this series

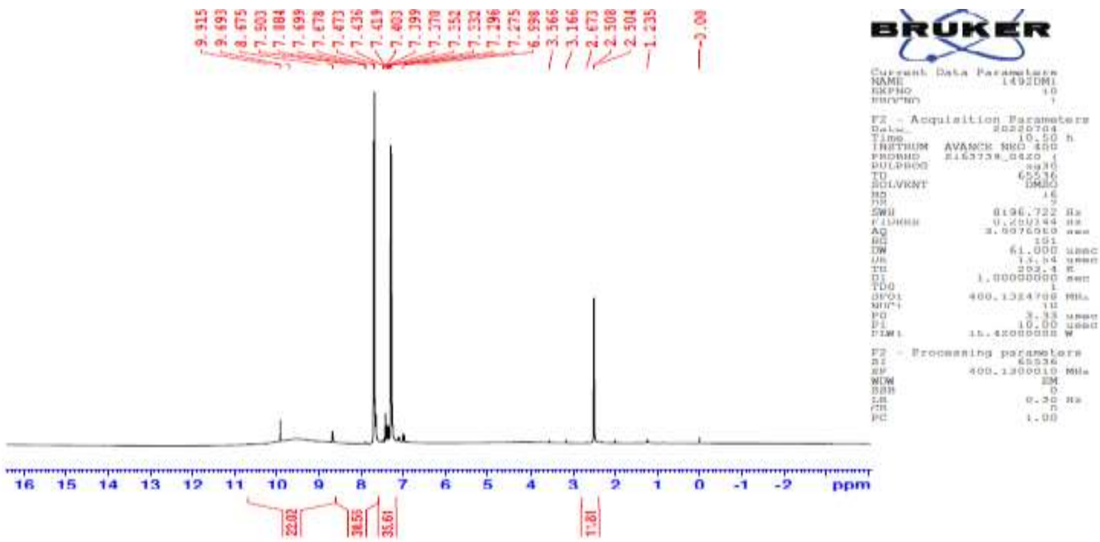

Fig. 8. The [1]H NMR of Schiff base (6)

The [1]H-NMR (300 MHz, DMSO-*d*6) of Schiff base (6) as representative for these series was shown in Fig. 8.

Conclusion

This paper summarizes the recent one-pot synthesis of seven Schiff bases by reaction of glucose with the appropriate amines via a conventional procedure, (Method A), which offered yields percentages of about 60-79% using the homogenous catalyst (acetic acid) in refluxing ethanol solvent for three hours. Correspondingly, the using of a heterogeneous catalyst of Deep eutectic solvent (Reline) (prepared from one mole choline chloride with two moles urea (Method B) can have a triple advantage of enhancing the percentages yields to 88-95%, eliminating the use of solvent and that this facilitates the reactions by reducing the refluxing time to one-third (only one hour).

Acknowledgment

Authors thank University of Mosul and Alnoor University College for financial support and facilities that provided for the completion this article.

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ŞİFF ƏSASLARININ QLÜKOZA VƏ MÜXTƏLIF AMINLƏRDƏN SİNTEZİNDƏ (RELINE) EVTEKTİK HƏLLEDİCİNİN KATALITİK SİSTEM KİMİ İSTİFADƏSİ

Zeynəb M. Mahmud[1] , Şakir M. Səid[2] , Mohanad Y. Saleh[3]

[1]*Təhsil Nazirliyi, Ninova Təhsil Müdirliyi*
[2]*Əczaçılıq Departamenti, Əl-Nur Universiteti Kolleci, Mosul, İraq*
[3]*Kimya Departamenti, Təmiz Elmlər üçün Təhsil Kolleci, Mosul Universiteti, Mosul, İraq*
e-mail: albdranyzynb@gmail.com; shakir.mahmood@alnoor.edu.iq;*mohanadalallaf@uomosul.edu.iq

Xülasə: İşdə iki müxtəlif üsulla yeddi yeni Şiff əsasları alınmışdır. Ənənəvi (A) metodunda qlükozanın sulu məhlulu və aminin spirtli məhlulu ekvimolekulyar miqdarda götürülərək üç saat ərzində qaynadılmışdır. (B) metodunda isə bir mol xolin xloriddən və iki mol sidik cövhərindən alınmış dərin evtektik həllediciden (Reline) katalizator kimi istifadə edilmişdir. Ənənəvi (A) üsulunda reaksiyanın çıxımı 60-79%, dərin evtektik həllediciden (Reline) istifadə edilən katalitik (B) üsulda çıxım isə 88-95% olduğu müəyyən edilmişdir. (Reline) dərin evtektik həllediciden ibarət olan katalitik sistem ekoloji cəhətdən təhlükəsizdir və üçqat üstünlüyə malikdir. Buraya faiz çıxımının artması, həllediciden istifadə olunmaması və geri axın müddətinin üç dəfəyə qədər azaltmaqla (yəni cəmi bir saat ərzində) reakiyanın sürətinin artması aid edilir.
Açar sözlər: qlükozamin Şiff əsasları, dərin evtektik həlledicilər, azometan, α- və β-qlükozaminlər.

ЭВТЕКТИЧЕСКИЙ РАСТВОРИТЕЛЬ (RELINE) КАК КАТАЛИТИЧЕСКАЯ СИСТЕМА В СИНТЕЗЕ ШИФФОВЫХ ОСНОВАНИЙ ИЗ ГЛЮКОЗЫ И РАЗЛИЧНЫХ АМИНОВ

Зайнаб М. Махмуд[1], Шакир М. Саид[2], Моханад Ю. Салех[3]

[1]*Министерство образования, Управление образования Ниневии*
[2]*Фармацевтический факультет Университетского колледжа Аль-Нур, Мосул, Ирак*
[3]*Кафедра химии, Педагогический колледж чистой науки, Мосульский университет, Мосул, Ирак*
e-mail: albdranyzynb@gmail.com; shakir.mahmood@alnoor.edu.iq;*mohanadalallaf@uomosul.edu.iq

Резюме: В работе были получены семь новых Шиффовых оснований двумя способами. В традиционном методе (А) эквимолекулярный водный раствор глюкозы и спиртовой раствор амина кипятили с обратным холодильником в течение трех часов, а в методе (Б) использовали глубокий эвтектический растворитель (Reline), полученный из одного моля хлорида холина и двух молей мочевины, в качестве катализатора. Было установлено, что процентный выход реакции в обычном методе (А) составляет 60-79%, а в каталитическом методе (Б) с использованием глубокоэвтектического растворителя (Reline) выход достигал 88-95%. Каталитическая система с глубоким эвтектическим растворителем (Reline) является экологически чистой средой, имеет тройное преимущество, заключающееся в повышении процентного выхода, исключении использования растворителя, и ускорения реакции за счет сокращения времени кипячения с обратным холодильником до трех раз (т.е. всего за один час).
Ключевые слова: глюкозоаминные Шиффвы основания, глубокие эвтектические растворители, азометан, α- и β-глюкозоамины.