ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 3, pp. 509–513. © Pleiades Publishing, Ltd., 2020.

Sugar-Catalyzed Synthesis of Triarylimidazoles—An Exemplary Model of Sweet Chemistry

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Received November 20, 2019; revised January 21, 2020; accepted January 21, 2020

Abstract—A fine, green, and efficient method has been proposed for the synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles using various sugars such as glucose, fructose, sucrose, lactose, and maltose as catalysts. The syntheses were carried out under very mild conditions in ethanol at room temperature, and the products were isolated in almost quantitative yield with a high purity.

Keywords: triarylimidazoles, sweet chemistry, sugars, green catalysts

DOI: 10.1134/S1070428020030227

Imidazoles (including benzimidazoles) play a vital role in life processes and are structural fragments of enzymes, vitamins, and various pharmacologically important drugs [1, 2]. Several triarylimidazoles proved to be biologically active compounds efficient as antibacterial [3, 4], antitumor [5], and antifungal agents [6, 7], glucagon receptor antagonists [8], plant growth regulators [9, 10], p38 MAP kinase inhibitors [11], B-Raf kinase inhibitors [12], as well as antihelmintic [13] and antithrombotic agents [2]. In addition, the utility of triarylimidazoles as photosensitive compounds in photography has been reported [14, 15].

Triarylimidazoles are typically synthesized by multicomponent condensations of 1,2-diketone, α-hydroxy ketone, or α-keto oxime with an aldehyde and ammonia (or ammonium salt) under pressure [16]. In the light of literature, a number of catalysts have been used in these reactions, e.g., amino acids [17], acetic acid [18–20], ionic liquids [21], ceric ammonium nitrate [22], silica-supported sulfuric acid [23], sodium bisulfite [24], iodine [25], $InCl_3 \cdot 3H_2O$ [26], *p*-toluenesulfonic acid [27], $Yb(OTf)_3$ [28], $NiCl_2 \cdot 6H_2O/Al_2O_3$ [29], etc. Most of the reported synthetic strategies involve expensive catalysts, multistep procedures, and tedious workup.

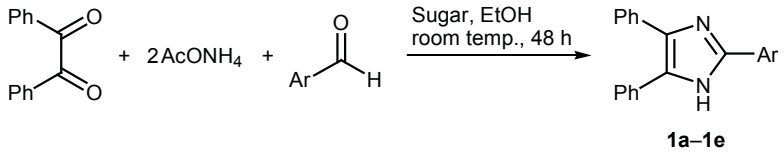
Therefore, search for low cost, environmentally benign, and efficient catalyst is the subject of extensive studies. Boysen [30] reported that sugar molecules can be perfect candidates due to the plenty hydroxyl groups they have which are capable to catalyze various reactions. The structural diversity of carbohydrates and the high density of functional groups offer a wide variety of opportunities for derivatization and tailoring of synthetic tools to a specific problem and their usage as catalysts in organic syntheses.

Zong et al. [31] prepared a "sugar catalyst" from D-glucose and investigated in detail its structure and catalytic properties. This was the first time that sugar catalyst was applied for the effective production of biodiesel from waste oils. The outcome of the application of sugars as a catalyst indicated that they are highly effective, minimally polluting, and reusable catalysts.

Exploiting this concept, herein we have successfully employed various sugars as catalysts for the synthesis of triarylimidazoles with a simple workup procedure.

In a model reaction, a mixture of benzil, benzaldehyde, and ammonium acetate was stirred in ethanol using "everyday" milk powder as a catalyst (Scheme 1). The product, 2,4,5-triphenyl-1*H*-imidazole

Scheme 1.



Ar = Ph (**a**), 2-HOC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), furan-2-yl (**e**).

(**1a**), was obtained in almost quantitative yield (99%) with a high purity.

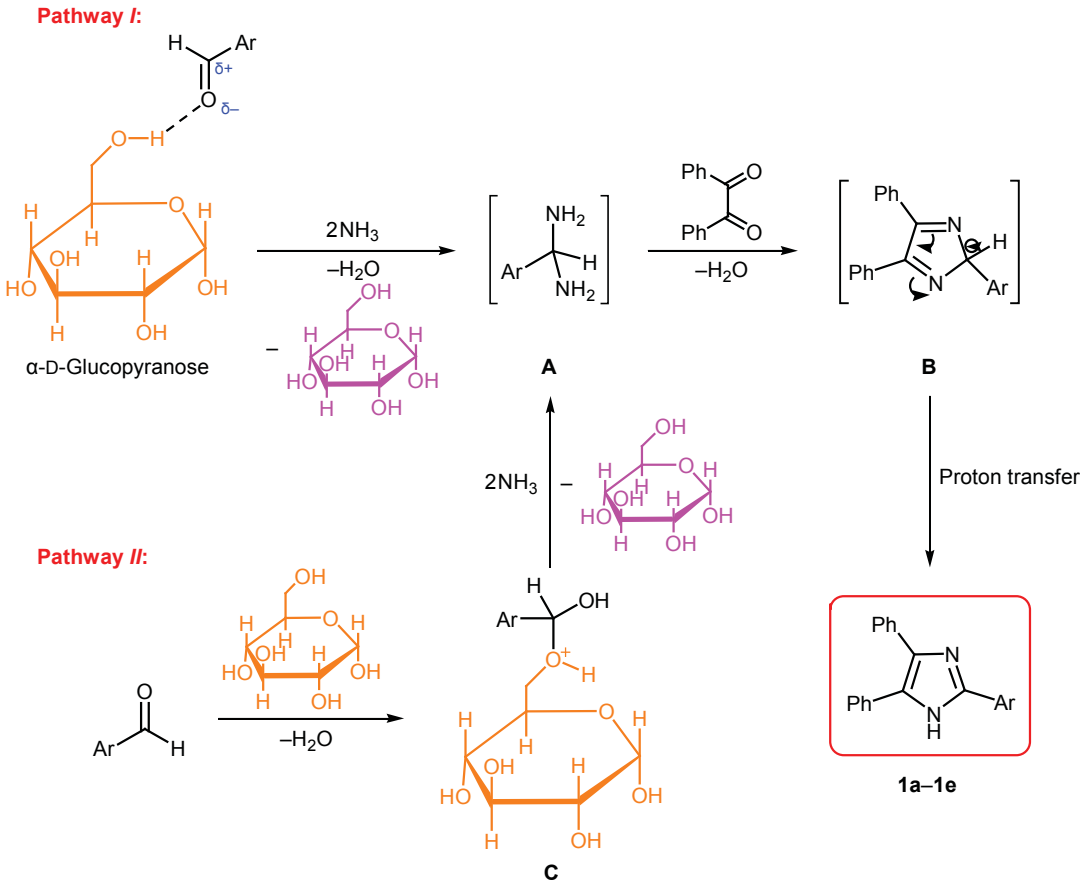
Sugars are major components of milk powders. This prompted us to use various sugars for catalyzing the synthesis of 2,4,5-triaryl-1*H*-imidazoles. A general synthetic procedure consists of stirring a mixture of benzil and aromatic aldehyde at a ratio of 1:1 in the presence of excess ammonium acetate and a catalytic amount of sugar at room temperature for 48 h using ethanol as solvent (Scheme 1). The products were obtained in high yields with a high purity (Table 1). Since sugars are soluble in water, the catalyst can be readily removed by simply washing with water.

A plausible mechanism for the glucose-catalyzed (as an example of sugar catalysts) synthesis of 2,4,5-triaryl-1*H*-imidazoles **1a**–**1e** is outlined in Scheme 2. The reaction may proceed through the formation of diamine intermediate **A** which can be formed along two different pathways *I* and/or *II*. Path *I* involves activation of the aldehyde carbonyl oxygen atom by glucose via intermolecular hydrogen bonding and subsequent condensation with two ammonia molecules to form diamine intermediate **A**. According to pathway *II*, diamine **A** is formed through oxonium intermediate **C**. The condensation of diamine **A** with the carbonyl groups of benzil and the subsequent dehydration gives

Table 1. Sugar-catalyzed syntheses of 2-aryl-4,5-diphenyl-1*H*-imidazoles **1a**–**1e** by reaction of benzil with aromatic aldehydes and ammonium acetate at room temperature in ethanol for 48 h

Aldehyde	Sugar catalyst	Product	Yield, %
Benzaldehyde	Glucose	**1a**	97
	Fructose		97
	Sucrose		98
	Lactose		97
	Maltose		96
Salicylaldehyde	Glucose	**1b**	96
	Fructose		97
	Sucrose		99
	Lactose		96
	Maltose		95
4-Chlorobenzaldehyde	Glucose	**1c**	97
	Fructose		98
	Sucrose		98
	Lactose		97
	Maltose		94
4-Nitrobenzaldehyde	Glucose	**1d**	98
	Fructose		98
	Sucrose		99
	Lactose		96
	Maltose		95
Furfural	Glucose	**1e**	98
	Fructose		99
	Sucrose		99
	Lactose		97
	Maltose		96

Scheme 2.



cyclic diimine **B** which rearranges to afford final 2,4,5-triaryl-1*H*-imidazole **1**.

Table 2 compares the yields of 2,4,5-triaryl-1*H*-imidazoles obtained by using various catalysts under different conditions. The sugar-catalyzed syntheses of compounds **1a**–**1e** proposed in this work provided higher yields than did some previously reported procedures.

Thus, the proposed sugar-catalyzed protocol makes it possible to synthesize highly pure 2,4,5-triaryl-1*H*-imidazoles in excellent yields under mild and green conditions. Presumably, this procedure can be extended to other diketones and aldehydes.

EXPERIMENTAL

Commercially available chemicals from Merck or Fluka were used as such or purified by simple techniques if necessary. The FT-IR spectra were taken on a Bruker Tensor-27 instrument. The melting points were measured with a Gallencamp apparatus and are

Table 2. Yields of 2,4,5-triaryl-1*H*-imidazoles obtained using different catalysts

Entry no.	Catalyst	Yield, %	Reference
1	Microwave irradiation	89–93	[33]
2	Boric acid $B(OH)_3$	50–90	[34]
3	Natural scolecite	57–78	[35]
4	Ammonium metavanadate NH_4VO_3	91	[36]
6	Chitosan as biodegradable solid acid catalyst	80–91	[37]
7	Benzyl(triphenyl)phosphonium chloride (BTPPC)	92	[38]
8	Lactic acid	17–63	[39]
9	Silica-supported Caro's acid	89–93	[40]
10	Sugars	95–98	Present study

uncorrected. The ^{1}H NMR spectra were recorded on a Bruker DPX instrument at 400 MHz. The high resolution mass spectra (electrospray ionization) were taken on a Finnigan MAT 312 mass spectrometer.

General procedure for the synthesis of 2,4,5-triaryl-1*H*-imidazoles 1a–1e. A mixture of benzil (0.525 g, 2.5 mmol), aromatic aldehyde (2.5 mmol), ammonium acetate (0.5 g, 6 mmol), and a sugar catalyst (0.05 g) in ethanol (10 mL) was stirred for 48 h at room temperature. After completion of the reaction (TLC), the product was filtered off, washed with water and cold ethanol, and dried until constant weight.

2,4,5-Triphenyl-1*H*-imidazole (1a). mp 275–276°C; published data [40]: mp 276–277°C. IR spectrum, ν, cm^{-1}: 3430, 2982, 1600, 1588, 1488, 1462, 1324. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 12.59 s (1H), 7.9 d (2H, J = 7.6 Hz), 7.47 d (4H, J = 6.8 Hz), 7.38 t (2H, J = 7.4 Hz), 7.32–7.22 m (7H). Mass spectrum: m/z 296 $[M]^+$.

2-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (1b). mp 191–193°C; published data [32]: mp 202–203°C. IR spectrum, ν, cm^{-1}: 3550, 3434, 3010, 1601, 1584, 1487, 1442, 1321. ^{1}H NMR (DMSO-d_6), δ, ppm: 13.0 s (1H), 10.25 s (1H), 8.02 d.d (1H, J = 1.4, 7.8 Hz), 7.54–7.25 m (10H), 7.0–6.92 m (3H). Mass spectrum: m/z: 312 $[M]^+$.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (1c). mp 258–259°C; published data [40]: mp 260–262°C. IR spectrum, ν, cm^{-1}: 3476, 3012, 1602, 1588, 1485, 1461, 1323. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 12.74 s (1H), 8.09 d (2H, J = 8.8 Hz), 7.55–7.22 m (12H). Mass spectrum: m/z 330/332 (I_{rel} 100/37%) $[M]^+$.

2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (1d). mp 222–224°C; published data [40]: mp 232–233°C. IR spectrum, ν, cm^{-1}: 3390, 2994, 1599, 1581, 1484, 1441, 1509, 1332. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.12 s (1H), 8.36–8.31 m (4H), 7.53–7.25 m (10H). Mass spectrum: m/z 341 $[M]^+$.

2-(Furan-2-yl)-4,5-diphenyl-1*H*-imidazole (1e). mp 188–189°C; published data [24]: mp 199–201°C. IR spectrum, ν, cm^{-1}: 3437, 2982, 1602, 1583, 1525, 1487, 1447, 1327. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.35 s (1H), 7.61 br.s (1H), 7.45–7.24 m (10H), 6.99 d (1H, J = 3.2 Hz), 6.52 m (1H).

FUNDING

This work was supported by research funding from Higher Education Commission, Pakistan (grant no. SRGP 1390).

CONFLICT OF INTEREST

No conflict of interest is declared by the authors.

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