Journal of Molecular Catalysis A: Chemical 370 (2013) 117–122

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Controllable selectivity in Biginelli and Hantzsch reactions using nanoZnO as a structure base catalyst

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ARTICLE INFO

Article history:
Received 23 May 2012
Received in revised form 5 December 2012
Accepted 9 December 2012
Available online 20 December 2012

Keywords:
Dissociation of urea
DHPMs
14-DHPs
NanoZnO
Biginelli
Hantzsch

ABSTRACT

Preparative nanoZnO and ZnO have been found as reusable catalysts for either condensation or dissociation of urea to ammonia and controllable selectivity in the Biginelli and Hantzsch reactions. The feasibility of urea dissociation to ammonia and switching of the selectivity of heterocyclization for DHPMs to DHPs over various metal oxides has been comparatively investigated. In the presence of nanoZnO and ZnO, direction of the MCR reaction in either Biginelli or Hantzsch way is possible by choice of the reaction conditions. Biginelli reaction occurs at 60 °C under solvent-free conditions, while Hantzsch reaction occurs in water at ~120–140 °C or under microwave irradiation using 5 mol% nanoZnO or 10 mol% ZnO.

1. Introduction

Multicomponent reactions (MCR) have performed quantitative revolutions in molecular architecting, access to multifunctional molecules, and combinatorial chemistry in recent years [1–3]. Biginelli and Hantzsch reactions are of great interest MCRs which in a single step afford dihydropyrimidin-2(1H)-ones (DHPMs) and 1,4-dihydropyridines (DHPs) as essential pharmaceuticals for calcium channel stimulating [4–8]. Although Biginelli and Hantzsch reactions are familiar in two components and their products are aza-analogous, they are varied in nitrogen sources. Urea, thiourea, and guanidine are used in the Biginelli reaction, while ammonia, ammonium salts, or atypically urea are nitrogen providers of DHPs in the Hantzsch reaction [9–11]. To improve both reactions, various acidic or basic catalysts and energy sources have been well documented [12–19,9,20–22].

In spite of the similarity in the starting materials and opportunity of the competition between Biginelli and Hantzsch reactions the feature of their borderlines is not clear [21]. According to the proposed mechanisms for base- or acid-catalyzed Biginelli reaction, urea, as a very cheap nitrogen source, condenses with other components to produce the DHPM products. Urea can be also dissociated to ammonium salts or ammonia at acidic or basic conditions [23,24], and thus the opportunity of the competition between Biginelli and Hantzsch reactins increases in these cases. However, by proper choice of catalyst and conditions, dissociation or condensation of urea and hence Biginelli or Hantzsch reaction would be optioned. Where condensation of urea with aldehyde and 1,3-dicarbonyl components occurs slower than dissociation of urea, the Biginelli reaction turns to the Hantzsch reaction and a divergent switching for Hantzsch/Biginelli is possible by utilize of urea as nitrogen provider of the DHP ring in Hantzsch reaction.

Metal oxide promoted organic transformations is a proficient subdivision of heterogeneous reactions which were highlighted by the use of nanosized metal oxide catalysts [25]. Stability under reaction conditions, dual acid/base properties of metal oxides, reusability, non toxicity, and non-hygroscopic properties make metal oxides much favorite catalysts. Zinc oxide (ZnO) is a low-priced metal oxide which professionally catalyzes various organic transformations [26–32]. Due to the easiness of preparation, various nanoZnO such as nanopowder, nanofluids and nanoparticles have been artificially prepared and used as reaction promoters [29–33]. Recently, we have prepared and used nanoZnO as efficient catalysts in organic reactions which in adsorption of the starting materials on the ZnO surface together with the coordination of accessible zinc cation to functional groups led to the activation and enhancement of the reaction rates and yields [27–29,34]. The powerful interaction of urea with ZnO [23] and efficient microwave-assisted dissociation of urea over ZnO [24] prompted us to evaluate the catalyst-control dissociation/condensation of urea and switching of the Biginelli/Hantzsch reactions. This can be also helped to verify the borderlines of these well-known MCRs (Scheme 1).

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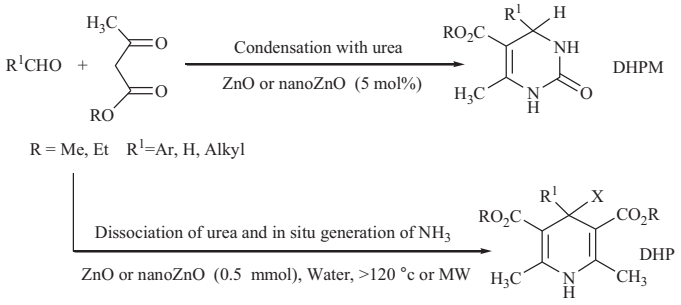
http://dx.doi.org/10.1016/j.molcata.2012.12.005



Scheme 1. Controllable Biginelli/Hantzsch reactions using nanoZnO catalyst.

2. Experimental

2.1. Preparation of nanoZnO

NanoZnO was prepared through the previously reported procedures [28–30]. Zinc acetate dihydrate (5.5 g) was dissolved in 50 mL of deionized water and then solid NaOH (16 g) was added slowly into the solution under magnetic stirring at room temperature. A transparent $Zn(OH)_4$ solution was formed. Then 2 mL of ionic liquid 1-butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) imide ([bmim][NTf_2]) was added to 3 mL of the above solution. The suspension was put into a domestic microwave oven (850 W) in air, 30% of the output power of the microwave was used to irradiate the mixture for 5 min (on for 10 s and off for 5 s). The white precipitate was collected by centrifugation, washed with deionized water and ethanol several times, and dried in vacuum oven at 40 °C for 10 h.

2.2. General procedure for the ZnO-catalyzed Biginelli reaction

To a mixture of aldehyde (2 mmol), ethyl acetoacetate (2 mmol), and either urea, thiourea or guanidine (2.5 mmol) was added ZnO (10 mol%) or nanoZnO (5 mol%) and the mixture was stirred at 60 °C under solvent-free conditions for the given times (Table 1). After the completion of the reaction (TLC monitoring), EtOAc (2× 10 mL) was added and the precipitated ZnO was filtered off. The resulting organic solution was washed with 10% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated to give the DHPM product. The products were structurally assigned by their IR, ^{1}H NMR, ^{13}C NMR spectra analysis and comparison to authentic samples.

2.3. General procedure for the nanoZnO-catalyzed Hantzsch reaction

To a mixture of aldehyde (2 mmol), ethyl acetoacetate (4 mmol), and urea (1.2 mmol) in water (1 mL) was added nanoZnO (0.5 mmol) or ZnO (1 mmol) and the mixture was irradiated by microwave or stirred at 140 °C for the given times (Table 2). After completion of the reaction (TLC monitoring), EtOAc (2× 10 mL) was added and the precipitated catalyst was centrifuged and filtered off. The resulting organic solution was washed with 10% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated to give the desired DHP product. The structure of products was assigned by analysis of their IR, ^{1}H NMR, ^{13}C NMR spectra and comparison to authentic samples.

2.4. Reusability of catalyst

ZnO or nanoZnO was regenerated by washing with EtOAc and drying at 300 °C or microwave irradiation and reused for three consecutive times in both Biginelli and Hantzsch reactions with no significant decreasing in reaction yields (Table 3).

2.5. Selected spectral data

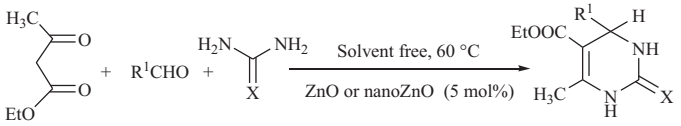
2.5.1. Ethyl 6-methyl-2-oxo-4-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 1, entry 3)

White powder, mp = 209–210 °C. FT-IR: υ_{max} (KBr) 3231, 3094 (*NH* stretching), 1649, 1701 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.1 (t, J = 7 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.98 (q, J = 7 Hz, 2H, CH_2CH_3), 5.11 (d, J = 3.5 Hz 1H, *CH*), 7.12 (s, 4H, H_{arom}), 7.67 (s, 1H, *NH*), and 9.14 (s, 1H, *NH*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.6, 18.2, 21.1, 54.2, 60.0, 100.0, 126.7, 129.4, 136.8, 142.5, 148.5, 152.5, and 166.2 ppm.

2.5.2. Ethyl 6-methyl-2-oxo-4-phenyl-2-thioxopyrimidine-5-carboxylate (Table 1, entry 12)

Pale yellow solid, mp = 203–205 °C. FT-IR (KBr): υ_{max} (KBr) 3328, 3186 (*NH* stretching), 1665 (C=O), 1200 (C=S) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6,): δ = 1.15 (t, J = 7.0 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.00 (q, J = 7 Hz, 2H, CH_2CH_3), 5.21 (s, 1H, *CH*), 7.20–750 (m, 5H, Ph), 9.60 (br s, 1H, *NH*), and 10.14 (br s, 1H, *NH*) ppm. ^{13}C NMR

Table 1
Zinc oxide-catalyzed synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones.



Entry	R^1	X	Yield (%)[a]	Time (h)	Mp (°C) Found (Reported)
1	C_6H_5	O	95	10	204–206 (200–203) [11]
2	4-$MeOC_6H_4$	O	95	10	209–210 (200–202) [11]
3	4-MeC_6H_4	O	94	10	206–209 (215–216) [11]
4	4-$N(Me)_2C_6H_4$	S	93	12	209–211 (209–210) [35]
5	4-$N(Me)_2C_6H_4$	O	95	11	248–250 (228–230) [36]
6	2-OHC_6H_4	S	89	12	206–209 (206–208) [35]
7	4-$NO_2C_6H_4$	O	67[b]	12	207–210 (208–211) [11]
8	4-ClC_6H_4	O	59[b]	12	209–212 (210–212) [11]
9	4-FC_6H_4	O	68[b]	12	184–185 (186–188) [35]
10	3,4-$(MeO)_2C_6H_3$	S	82	12	212–215 (212–214) [35]
11	C_6H_5	*NH*	90	14	175–179 (176–178) [35]
12	C_6H_5	S	87	16	203–206 (203–205) [37]

[a] Isolated yield.
[b] As a part of the 3,4-dihydropyrimidin-2(1*H*)-one and 1,4-DHP mixture which was isolated by crystallization.