Journal of Saudi Chemical Society (2017) 21, S305–S310

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis of new annulated pyrano[2,3-*d*]pyrimidine derivatives using organo catalyst (DABCO) in aqueous media

Ajmal R. Bhat [a], **Aabid H. Shalla** [b], **Rajendra S. Dongre** [a,*]

[a] *Department of Chemistry, RTM Nagpur University, Nagpur 440033, India*
[b] *Islamic University of Science and Technology, Kashmir 192122, India*

Received 5 November 2013; revised 13 March 2014; accepted 21 March 2014
Available online 3 April 2014

KEYWORDS

Aromatic aldehydes;
Ethylcyanoacetate;
Barbituric acid;
Ethanol:water;
Pyrano[2,3-*d*]pyrimidines;
DABCO catalyst

Abstract A selective method for the synthesis of annulated pyrano[2,3-*d*]pyrimidines has been developed. It was shown that base catalysis is more efficient in this reaction, rather than acid catalysis as it is believed that 1,4-diazabicyclo[2.2.2]octane (DABCO) is N-type base catalyst used for the synthesis of pyrano[2,3-*d*]pyramidine derivatives via one-pot three component condensation reactions of various aromatic aldehydes, active methylene compounds and barbituric acid in aqueous ethanol carried at normal temperature. The potential application of DABCO in organic synthesis increasing rapidly because of its reaction simplicity, less pollution, and minimum reaction time, high yields of the biological active products, uses less toxic solvents and low cost chemicals.

1. Introduction

Multicomponent reactions (MCRs) have enormous benefit with their high yields of products, ease of execution in the aim of analysis of combinatorial chemistry [32]. However, in the past decade there has been tremendous development in three- and four-component reactions and great efforts were taken to develop new MCRs [29,7]. Solid-phase organic synthesis is a background of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug molecules. Many organic solvents are harmful and their use should therefore be minimized as far as possible. Green alternatives under investigation for organic reactions are water [8,11], supercritical fluids, in particular CO_2 [19] and solvent-free condition (SFC) [23]. The use of water as the reaction medium exhibits a significant advantage because this green solvent is highly polar and therefore immiscible with most organic compounds [21]. Moreover the water-soluble catalyst resides and operates in the aqueous media, and separation of organic compounds is thus easy. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple work up, comparatively cheaper to operate and particularly important in industry. Thus, there is a need for developing multicomponent reactions (MCR's) in aqueous ethanol and without the use of harmful organic solvent.

* Corresponding author. Tel.: +91 8087723120.
E-mail address: rsdongre@hotmail.com (R.S. Dongre).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2014.03.008

The synthesis of fused heterocycles has attracted considerable interest in heterocyclic chemistry as the fusion of biodynamic heterosystems has proved to be very attractive and constructive for the design of a new molecular framework of potential drugs with varying pharmacological activities. A major challenge of the modern synthetic chemistry is to design highly efficient chemical reaction sequences which provide molecules containing maximum complexity and structural diversity with interesting bioactivities in minimum number of synthetic steps. Recently, organocatalyst has increased extremely in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and the selectivity of many organocatalyst reactions meet the standards of established organic reactions. One of these organo catalysts is the 1,4-diazabicyclo[2.2.2]octane (DABCO) which has received considerable attention as an inexpensive, eco-friendly, high reactive and non-toxic base catalyst for various organic synthesis, affording the corresponding products in excellent yields with high selectivity. Pyrano[2,3-*d*]pyrimidine is unsaturated six membered heterocycle which is formed by fusion of pyran and pyrimidine rings together, consisting of one oxygen atom at position number 8 and two nitrogen atoms at position number 1 and 3 respectively. If pyrano[2,3-*d*]pyrimidine moieties are clubbed into one molecule, then resultant derivative enhances its pharmaceutical activity as abundant in biologically active compounds such as antitumour [2], cardiotonic [12], antibronchitic [17] and antifungal activity [26]. Some of them exhibit antihypertensive activity [6], antimalarial [9], analgesic [20,30]; and antiviral evaluation [27] properties. Pyrano[2,3-*d*]pyrimidines are building blocks used to evaluate their antimicrobial activities and various derived natural products are also used as a drug for insomnia treatment [24]. Therefore, for the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of pyrano[2,3-*d*]pyrimidine derivatives. As a result, a number of reports have appeared in the literature which usually requires forcing conditions, long reaction times and complex synthetic pathways. Pyrano[2,3-*d*]pyrimidine synthesis was reported under various conditions such as microwave irradiation [10,13], ultrasonic irradiation [18], solvent free condition and in aqueous medium in the absence of catalysts [14]); sulfonic acid nanoporous silica (SBA-Pr-SO_3H) [34], diammonium hydrogen phosphate (DAHP) [3], L-proline (Heravi et al., 2010); [5], $H_{14}[NaP_5W_{30}O_{110}]$ (Heravi et al., 2010), ionic liquids [33]. Reported methods appearing in the literature usually require forcing conditions, long reaction time, create wastes, need complex synthetic pathway and involved organic solvents as well high energy to proceed. So, due to environmental concerns associated with aspects of organic solvents, development of aqueous phase synthesis of pyrano[2,3-*d*]pyrimidines is of considerable interest in this research to cater short reaction time, environmentally friendly procedure and excellent yields by this proposed route. Aqueous ethanol (ethanol:water) in place of organic solvents was used besides being non-hazardous, it is cheap, readily available and simple to handle so, we describe here a rapid, energy efficient, green and economically viable and easy (room temperature) protocol for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives by using DABCO catalyst (Scheme 1).

2. Materials and methods

All chemicals were obtained from Aldrich Chemical Co. and S.D. Finechem Co. and used without further purification. Melting points were determined by open capillary method and were uncorrected. ^{1}H NMR spectra were obtained on a BRUKER instrument (300 MHz). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 as solvent with TMS as internal standard. Chemical shifts are reported in ppm and mass spectra were measured using high resolution GC–MS (DFS) thermo spectrometers with EI (70 EV). Reactions have been monitored by thin layer chromatography on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor Scheme 2).

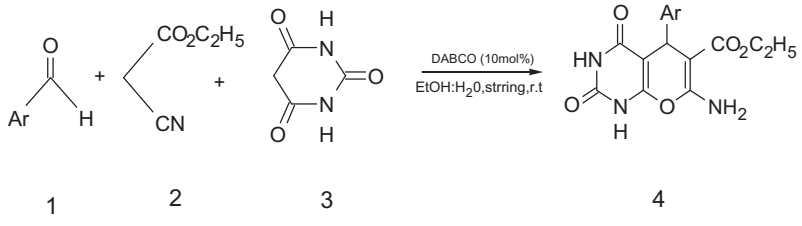
2.1. General procedure for the preparation of pyrano[2,3-d]pyrimidinones

Aromatic aldehydes (**1**), active methylene compound (**2**), barbituric acid (**3**) (2 mmol each) and 10 mol% 1,4-diazabicyclo[2,2,2]octane (DABCO) were taken in an RB flask with 15 ml solvent ethanol:water (1:1 ratio) mixture and stirred for 30–40 min at room temperature. The reaction was monitored by thin layer chromatography using eluent petroleum ether and ethyl acetate 7:3. The solid compound was filtered, washed with cold water and recrystallization from ethanol to obtain pure product pyrano[2,3-*d*]pyrimidine derivatives.

2.2. Spectral data for synthesized pyrano[2,3-d]pyrimidine products

*2.2.1. Ethyl7-amino-5-(4-methylphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4a**)*

IR (KBr, cm^{-1}): 3395, 3103, 2223, 1912, 1845, 1662, 1567, 1734, ^{1}H NMR (300 MHz, DMSO): δ 2.36 (s, 3H, CH3), 2.6 (s, 3H, CH_3), 4.13 (s, 1H, H-5), 5.21 (s, 2H, CH_2), 7.12 (m, 2H, H-Ar), 7.20 (m, 2H, H-Ar), 7.60 (br s, 2H, NH_2), 10.89 (s, 1H, NH), 11.43 (s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 20.9, 88.7, 98.3, 115.5, 127.5, 128.1,



Scheme 1 General synthesis of substituted pyrano[2,3-*d*]pyrimidinones.