Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 148 (2015) 175–183

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Regioselective synthesis and *ab initio* calculations of fused heterocycles thermally and under microwave irradiation

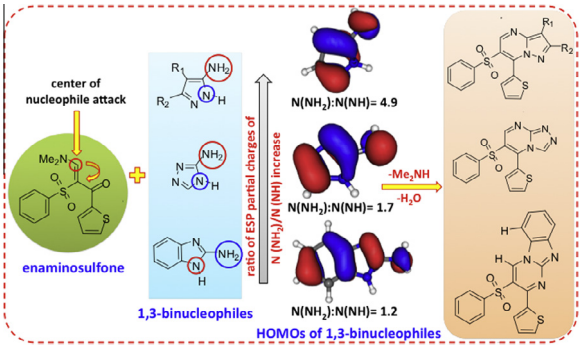
Mostafa E. Salem [a], Ashour A. Ahmed [a,b,c], Mohamed R. Shaaban [a,d], Mohamed F. Shibl [e,f,*], Ahmad M. Farag [a]

[a] Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
[b] Institute of Physics, Rostock University, 18051 Rostock, Germany
[c] Steinbeis GmbH & Co. KG für Technologietransfer, 70174 Stuttgart, Germany
[d] Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia
[e] Department of Materials Science and Engineering (MSE), Cornell University, Ithaca, NY 14853, USA
[f] Gas Processing Center, College of Engineering, Qatar University, P.O. Box 2713, Doha, Qatar

HIGHLIGHTS

- Biologically important heterocyclic systems have been synthesized from inexpensive starting materials.
- Microwave irradiation in addition to the conventional methods have been used in the synthesis.
- The regioselectivity of this cyclocondensation reaction has been revealed by DFT calculations.
- The reaction product is dependent on the nitrogen electron density of the 1,3-binucleophiles.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form 16 March 2015
Accepted 27 March 2015
Available online 2 April 2015

Keywords:
Regioselectivity
DFT calculations
Cyclocondensation
Sulfones
Alterative synthesis

ABSTRACT

Pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyrimidine, and pyrimido[1,2-*a*]benzimidazole, pyrido[1,2-*a*]benzimidazole ring systems incorporating phenylsulfonyl moiety were synthesized *via* the reaction of 3-(*N*,*N*-dimethylamino)-1-(thiophen-2-yl)-2-(phenylsulfonyl)prop-2-en-1-one derivatives with the appropriate aminoazoles as 1,3-binucleophiles and 1*H*-benzimidazol-2-ylacetonitrile using conventional methods as well as microwave irradiation. The regioselectivity of the cyclocondensation reactions was confirmed both experimentally by alternative synthesis of reaction products and theoretically using *ab initio* quantum chemical calculations namely the Density Functional Theory (DFT). The theoretical work was carried out using the Becke, three parameter, Lee–Yang–Parr hybrid functional (B3LYP) combined with the 6-311++G(d,p) basis set. It was found that the final cyclocondensation reaction product depends mainly on the initial addition to the activated double bond by the nitrogen atom of the 1,3-binucleophiles that has the higher electron density.

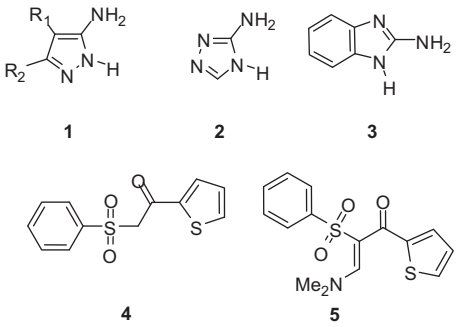
Introduction

Sulfones [1,2] are a versatile class of compounds due to their applications in many pharmaceutical fields [3–9]. They have

* Corresponding author at: Gas Processing Center, College of Engineering, Qatar University, P.O. Box 2713, Doha, Qatar. Tel.: +974 6608 2307.
E-mail address: mfshibl@qu.edu.qa (M.F. Shibl).

http://dx.doi.org/10.1016/j.saa.2015.03.102
1386-1425/

attracted the attention of many authors and great efforts have been made to develop new approaches to a variety of heterocycles incorporating phenylsulfonyl moiety for biological screening. Moreover, sulfone moiety is usually incorporated as an active part in many analgesic anti-inflammatory molecules available as drugs in the market such as celecoxib [2,10], valdecoxib [11], rofecoxib [12], parecoxib [13], etoricoxib [14], tenoxicam [15], piroxicam [16], meloxicam [17], lornoxicam [18], ampiroxicam [19], and nimesulide [20,21–23]. On the other hand, α-aminoazoles as 1,3-binucleophiles are quite important reagents in modern heterocyclic synthesis, and their reactions with electrophiles are the most widespread and facile synthetic approach to obtain diverse fused heterocyclic systems containing azole moiety [24–26]. In addition, aminoazoles and their ambident properties make them challenging objectives for studying mechanisms of organic reactions and then tuning their regioselectivity. The mostly investigated area of aminoazoles chemistry is their two component reactions with ketoesters, β-dicarbonyls, α,β-unsaturated aldehydes/ketones and enaminones yielding fused azoloazines [24–31]. Moreover, multicomponent reactions (MCRs) based on aminoazole building-blocks were covered in literature which are very promising for combinatorial and medicinal chemistry as well as for diversity-oriented synthesis [32]. In continuation of our recent work aiming at the synthesis of heterocyclic systems with remarkable biological importances [33–38], the utility of β-keto-β-sulfonylenamines as building blocks for the synthesis of pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidines, pyrimido[1,2-*a*]benzimidazole, and pyrido[1,2-*a*]benzimidazole under microwave irradiation is reported. In this work, several aminoazoles as 1,3-binucleophiles, namely; 5-amino-1*H*-pyrazoles **1**, 3-amino-1,2,4-triazole (**2**), and 2-aminobenzimidazole (**3**) are used in construction of the corresponding fused ring systems *via* their cyclocondensation with enaminosulfone, (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) as well as their MCR with the sulfone, 2-phenylsulfonyl-1-(thiophen-2-yl)-ethan-1-one (**4**) and triethyl orthoformate as a CH-acid.



The regioselectivity in such cyclocondensation reaction was examined using DFT quantum chemical calculations. Geometry optimizations have been performed for heterocyclic amines **1**, **2**, **3**, and the enaminosulfone **5**. The molecular geometries were fully optimized using the gradient minimization technique. The minima are characterized by having zero gradient norms and by diagonalizing the matrix of the second derivatives to give positive harmonic vibrational frequencies. This was done using the Becke, three parameter, Lee–Yang–Parr hybrid functional (B3LYP) [39] combined with the 6-311++G(d,p) basis set [40]. These calculations have been performed using the Gaussian09 program package [41]. The partial atomic charges on the first nucleophilic center N of NH_2 and the second nucleophilic center N of NH are calculated using Mulliken population analysis, atomic polar tensor (APT), and electrostatic potential (ESP).

Results and discussion

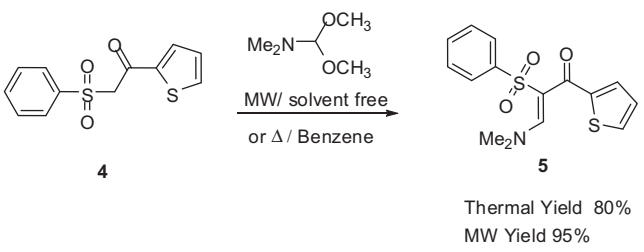
The versatile, *hitherto* unreported (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) was readily obtained by refluxing equimolar quantities of 2-phenylsulfonyl-1-(thiophen-2-yl)-ethan-1-one (**4**) and dimethylformamide dimethylacetal (DMF-DMA), without solvent under microwave irradiation or in benzene under conventional method as shown in Scheme 1.

The structure of the enaminosulfone **5** was confirmed by its elemental analysis and spectral data. For example, its ^{1}H NMR spectrum displayed a singlet signal at δ 3.33 due to *N*,*N*-dimethyl protons, a singlet signal at δ 7.91 due to olefinic proton, in addition to an aromatic and thiophene ring multiplets in the region δ 7.15–7.96.

The reactivity of the enaminosulfone **5**, in general, can be attributed to the delocalization of the lone pair of electrons on NMe_2 nitrogen (N) with the carbonyl carbon (C) as well as the conjugation with the sulfone group, see Fig. 1. These delocalization and conjugation effects result in two electron poor centers at N and C between which an electron rich carbon atom.

When (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) was treated with substituted 5-amino-1*H*-pyrazole derivatives **1a–c**, either under refluxing ethanol in the presence of a catalytic amount of piperidine or in pyridine under MW irradiation, it afforded, the corresponding 6-(phenylsulfonyl)-7-(thien-2-yl)pyrazolo[1,5-*a*]pyrimidine derivatives **7a–c** (Scheme 2) in a good yield as shown in Table 1. In general, the yields of the microwave synthesis are higher than the conventional heating as expected. The structures of **7a–c** were established on the basis of their elemental analyses and spectral data. For example, the mass spectrum of compound **7a**, revealed a molecular ion peak at *m*/*z* 451. Its ^{1}H NMR spectrum revealed a singlet signal at δ 7.52 due to pyrazole CH-3 proton and a singlet signal at δ 9.18 (pyrimidine-CH-5), in addition to aromatic protons as a multiplet at δ 7.25–8.02. The formation of **7a–c** is assumed to take place *via* an initial *Michael-type* addition of the exocyclic amino group in aminopyrazoles **1a–c** to α,β-unsaturated moiety in the enaminosulfone **5**, to yield the corresponding acyclic non-isolable intermediates **6a–c** which undergo intramolecular cyclization and aromatization into the final products **7a–c** under the reaction conditions (Scheme 2). The other expected product **8a–c** was ruled out on the basis of alternative synthesis of compounds **7a–c** theoretical investigations. Thus, solvent free one-pot, three component reaction of the sulfone **4**, aminopyrazoles **1b** (taken as a typical example), and triethyl orthoformate, afforded product identical in all respects (m.p., mixed m.p. and IR spectra) with the product obtained from the stepwise synthesis (Scheme 2).

DFT calculations show that the electron density on the first nucleophilic center, N of NH_2 ($N_{exocyclic}$), is more than that on the second nucleophilic center, N of NH ($N_{endocyclic}$), for the optimized



Scheme 1.