Journal of Molecular Structure 1142 (2017) 122–129

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Microwave assisted regioselective synthesis of novel pyrazoles and pyrazolopyridazines *via* fluorine containing building blocks

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ARTICLE INFO

Article history:
Received 12 December 2016
Received in revised form
8 April 2017
Accepted 12 April 2017
Available online 18 April 2017

Keywords:
Microwave irradiations
1,3-dipolar cycloaddition
Regioselectivity
Pyrazoles
Pyrazolo pyridazines

ABSTRACT

A facile regioselective synthesis of novel pyrazole derivatives containing a fluorophenyl moiety *via* the 1,3-dipolar cycloaddition of nitrileimines and enamines using conventional as well as microwave irradiation conditions have been achieved. Fluorine-containing building blocks methodology was used in order to access the targeted fluorinated compounds. The structures of the synthesized products were confirmed by ^{1}H NMR, FT-IR, mass spectrometry, and elemental analyses. Furthermore, the synthesized pyrazoles have been used in the synthesis of some new pyrazolo pyidazines containing pendent to fluorophenyl moiety. An unambiguous structural assignment of the obtained pyrazole regioisomers was determined using the ^{1}H NMR analysis as a valuable tool.

1. Introduction

The presence of fluorinated moieties in organic molecules may dramatically modifies the physicochemical profile of organic compounds [1]. Thus, fluorine containing heterocycles have attracted much interest because of their potent biological and pharmacological activities [2–4], and their role in the development of many functional materials [5–11]. Among these heterocycles, pyrazoles have been reported to have important biological activities [12], including; anti-nociceptive activities [13]; in some drugs for Parkinson's diseases [14] and cytotoxicity against cancer cell lines [15]. Also, many fluoro compounds are well-known commercialized drugs, such as Prozac, Casodex, Arava and Celebrex can be represented as shown in Fig. 1 [16].

Due to this chemotherapeutic importance, much more attention has been paid to develope of new synthetic methodologies to heterocycles pendent to fluorinated organic groups. However, most of the known methodologies applied to the synthesis of fluorinated organic molecules suffer from serious disadvantages. For example, common fluorinating agents are highly toxic and difficult to be handled at ambient conditions. Also, direct fluorination always lake of selectivity of reaction products [17–19]. Currently, other alternative routes are used including green methodologies such as electrochemical fluorination and using fluorine-containing building blocks which can be considered to be a cornerstone in the field of fluoro-organic compounds synthesis including our contribution in these fields [20–26]. On the other hand, microwave irradiation has been recently demonstrated its utility as an energy source to improve yields and/or save reaction conditions, especially in the field of heterocyclic synthesis [27]. The use of the pressurized microwave irradiation can be very advantageous to many synthetic approaches where the solvent can be heated up to temperatures that are 2–4 times their respective boiling points and thus providing large rate enhancement. In addition, keeping the atmosphere from moisture that may affect the moisture sensitive reagents decreases the possibility of formation of the undesired byproducts. Motivated by the aforementioned findings and as a part of our interest in the study and synthesis of a wide range of fluorinated heterocyclic systems, we report on the easy access of new pyrazoles and pyrazolo pyridazines pendent to fluorophenyl moiety *via* 1,3-dipolar cycloaddition of nitrileimines to the versatile 3-(dimethylamino)-1-(4-fluorophenyl)prop-2-en-1-one (**3**) under both microwave irradiation and conventional methods. Also unambiguously proof the structure of the obtained regioisomers utilizing the chemical evidences as well as spectral data.

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http://dx.doi.org/10.1016/j.molstruc.2017.04.047
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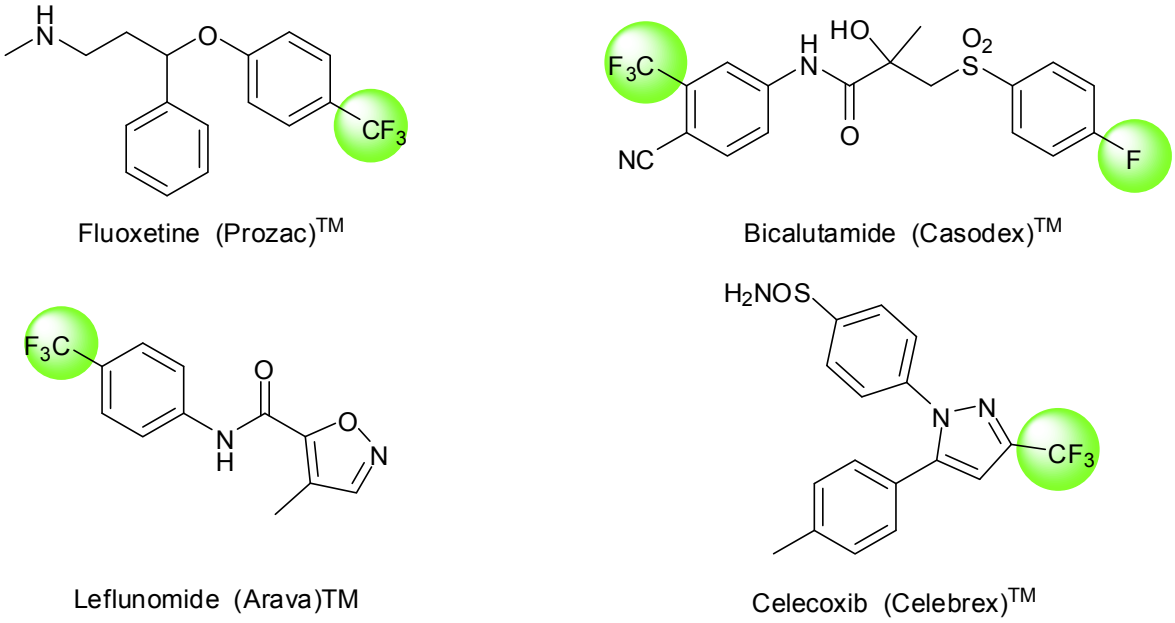

Fig. 1. Fluorinated commercialized drugs.

2. Experimental section

2.1. Materials and methods

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded on Shimadzu IR-3600 spectrometer (potassium bromide) ύ/cm^{-1}. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer (^{1}H NMR (300 MHz) and ^{13}C NMR (75.46 MHz)) were run in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Center of Cairo University, Giza, Egypt and recorded on Elementar-Vario EL automatic analyzer. The Microwave reactor was used in this work is the CEM mars machine. CEM has several vessel types that are designed for their ovens: Closed-system vessels including the HP-500 (500 psig material design pressure and 260 °C), pictured below, have liners are composed of PFA. Each reaction vessel fits within a microwave-transparent sleeve made of Kevlar, and each vessel-sleeve assembly gets clamped within a carriage or 'support module' with 5 foot-pounds of torque applied to the clamping bolt. Hydrazonoyl halides were prepared according to the reported literature [28].

2.1.1. Synthesis of 1-(4-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (3)

To a solution of *p*-fluoroacetophenone (**1**) (10 mmol) in xylene or without solvent was added dimethylformamide-dimethylacetal *(DMF-DMA)* (12 mmol) and the mixture was mixed in a HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 110 °C) for 10 min. The excess *DMF-DMA* was evaporated in *vacuo* and the residue was dissolved in ether (50 mL) and dried over $MgSO_4$. After evaporation of the solvent the resulting solid was recrystallized from hexane to afford (*E*)-1-(4-fluorophenyl)-3-(dimethylamino) prop-2-en-1-one (**2**), The physical and spectral data of the synthesized compound are listed below.

Mp.: 64–65 °C; IR (KBr) cm^{-1}: 1664 (C=O), 1598 (C=N); ^{1}H NMR ($CDCl_3$): δ 3.02 (s, 6H, N(CH_3)$_2$), 5.67 (d, 1H, J = 12.3 Hz, –CO–CH]), 7.10 (d, 2H, Ar–H), 7.80 (d, J = 12.3 Hz, 1H, =CH–N), 7.92 (d, 2H, Ar–H).; MS (*m/z*): 193 (M^+); $C_{11}H_{12}FNO$:Anal. Calcd: C, 68.38; H, 6.26; N, 7.25. Found C, 68.28; H, 6.16; N, 7.35. %.

2.1.2. Reactivity of 1-(4-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (3) towards nitrileimines: synthesis of novel pyrazoles

2.1.2.1. General procedure

2.1.2.1.1. Thermal method. To a mixture of 1-(4-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (**3**) (2 mmol) and the appropriate hydrazonoyl chloride **4a-i** or **11** (2 mmol), in benzene (20 mL), an equivalent amount of triethylamine was added. The reaction mixture was stirred at room temperature overnight or under reflux and followed by TLC then the solvent was distilled off under reduced pressure. The residual brown viscous liquid was taken in methanol and purified through a flash column of silica gel with ethyl acetate as an eluent. Evaporation of the solvent under reduced pressure afforded a pure solid, dried and finally recrystallized from heptane to afford corresponding pyrazole derivatives **7a-i** or **14**.

2.1.2.1.2. Microwave method. To a mixture of 1-(4-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (**3**) (2 mmol) and the appropriate hydrazonyl chloride **4a-i** or **11** (2 mmol), in benzene (20 mL), an equivalent amount of triethylamine was added. The reaction mixture was mixed in a HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (600 W, 17.2 bar, 85 °C) for a given time (followed by TLC). The solvent was distilled off under reduced pressure then the residual brown viscous liquid was taken in methanol and purified through a flash column of silica gel with ethyl acetate as an eluent. Evaporation of the solvent under reduced pressure afforded a pure solid, dried and finally recrystallized from heptane or hexane to afford corresponding pyrazole derivatives. The physical and spectral data of the synthesized compound are listed below.