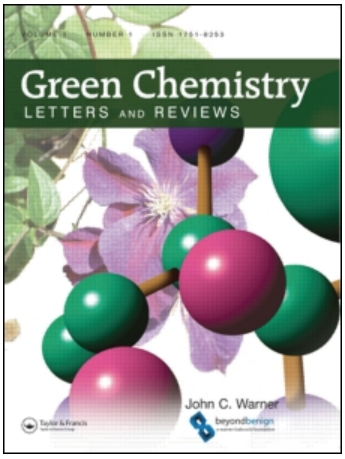

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An efficient method for Knoevenagel condensation: a facile synthesis of 5-arylidenyl 2,4-thiazolidinedione

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ORIGINAL ARTICLE

An efficient method for Knoevenagel condensation: a facile synthesis of 5-arylidenyl 2,4-thiazolidinedione

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Knoevenagel condensation of various aromatic aldehydes with 2,4-thiazolidinedione has been carried out in polyethylene glycol-300. The reactions were carried out at moderate temperature with very simple isolation procedure and with better yields.

Keywords: 5-arylidenyl 2,4-thiazolidinedione; 2,4-thiazolidinedione; Knoevenagel condensation; polyethylene glycol (PEG-300)

Introduction

2,4-Thiazolidinedione and its derivatives represent the most promising group of compounds having a variety of pharmacological features *(1,2)*. Different possibilities of heterocyclic modifications with a wide spectrum of pharmacological properties are the most important grounds for investigations of this interesting class of compounds. The fifth position of 2,4-thiazolidinedione (the methylene group) being relatively more reactive *(3,4)*; hence, most of the modification at 2,4-thiazolidinedione ring are done on the fifth position to build new molecules. 5-Arylidenyl 2,4-thiazolidinedione displays a wide spectrum of pharmacological properties *(5,6)*. A row of 5-arylidenyl 2,4-thiazolidinediones are under clinical trials as potential phospholipase A_2 inhibitor, dual COX-2/5-LOX inhibitor, and anti-inflammatory agents *(7)*.

Owing to the wide range of pharmacological activities, the synthesis of this compound has become an important target in the recent years. The synthetic methods leading to the 5-arylidenyl 2,4-thiazolidinediones are recently reviewed by Lesyk and Zimenkovsky *(7)*. The Knoevenagel condensation of the active methylene situated at the fifth position of the 2,4-thiazolidinedione with oxo compounds (aldehydes) under basic condition constitutes an efficient way to yield 5-arylidenyl 2,4-thiazolidinedione derivatives. It is reported that such condensations can be accelerated by sodium hydroxide *(8)*/sodium acetate in the presence of acetic acid or its anhydride *(9)* at 140–190°C *(10)*. Ammonium hydroxide *(11)* or its mixture with ammonium chloride *(12)*/methylamine in acetic acid *(13)* and morpholine in acetic acid *(14)* are also used to catalyze the reactions. Catalysts like pyridine *(15)*, piperdine *(16)*, piperdinium acetate or benzoate in alcohol *(17)*, piperdinium benzoate in toluene *(18)* and piperdine and acetic acid in toluene *(19)* have also been reported for the synthesis of 5-arylidenyl 2,4-thiazolidinediones. Some authors have also synthesized 5-arylidenyl 2,4-thiazolidinediones in the presence of K_2CO_3 in DMF, K_2CO_3 in DMSO, sodium acetate *(20)* in a mixture of DMF–AcOH, ammonium acetate *(21)* in toluene, ethylenediammonium diacetate *(22)* in methanol, NH_3 *(23)* in H_2O (25%) in ethanol, catalytic amount of piperdine *(24)* in ethanol, NH_4OH and NH_4Cl in ethanol, piperdine in toluene and dichloroethane using molecular sieves *(24)*. Villemin and co-workers *(25)* have reported the synthesis of 5-arylidenyl 2,4-thiazolidinediones by allowing the condensation of 3-methyl 2,4-thiazolidinedione with aromatic aldehydes on a surface of KF/Al_2O_3 in CH_2Cl_2 under microwave irradiation *(21,22)*.

Result and discussion

In the Knoevenagel condensation solvents are especially important, because they are generally used in large quantities. In the present work, attempt is made to modify the conditions of Knoevenagel condensation and we hereby report a very simple, green and highly efficient method for the condensation of

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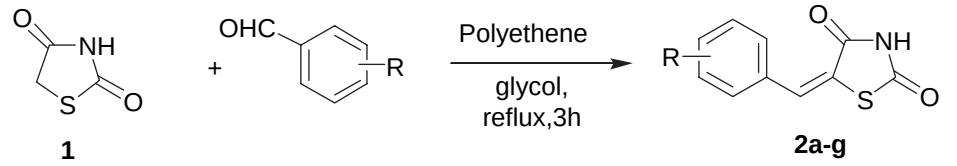


Scheme 1.

various aromatic aldehydes and 2,4-thiazolidinedione (Scheme 1). The reactions were carried out in polyethylene glycol (PEG) at moderate temperature and by avoiding the use of hazardous catalysts/bases like pyridine or piperdine, and solvents like toluene, methanol, DMF and DMSO. The PEGs are hydrophilic, thermally stable, non-toxic and protic solvents *(26)* having aprotic etheral sites and are able to dissolve most of the organic and some inorganic solutes *(27)*. This class of oligomers are established as green/cleaner host recyclable solvents *(28)* and also functions as safer phase transfer catalyst *(29,30)*. Different aromatic aldehydes and 2,4-thiazolidinedione in PEG-300 were heated on oil bath at 100–120°C (**2a–g**). All the reactions run rapidly and were found to furnish good yields of 5-arylidenyl 2,4-thiazolidinediones and no other byproducts were formed during the course of the reaction. In this course the etheral sites of PEG-300 might be displaying catalytical behavior as general bases and may facilitate the initial formation of carbanion/enolate from 2,4-thiazolidinediones and thereby helping to expedite the overall rate of the condensation. After completion of the reaction carried in PEG-300, the reaction mass was poured on ice water. After filtration, the obtained solid condensation product was further purified by crystallization. The aqueous filtrate was distilled at 100°C to remove water and thus separated PEG-300 was recycled and reused. The required starting material, i.e. 2,4-thiazolidinedione *(1)* was also prepared in an ecofriendly way, by the reaction of thiourea with chloro acetic acid in aqueous media.

In conclusion, we have demonstrated that the Knoevenagel condensation between aromatic aldehydes and 2,4-thiazaolidinedione (the active methylene group) can be effectively performed at moderate temperature in PEG media, which provides a simple route to the synthesis of 5-arylidenyl 2,4-thiazolidinedione. The present method has many obvious advantages compared to those reported in literature, including simplicity of the methodology, ease of product isolation, good yields, short reaction times, no use of catalyst, and being environmentally benign (Table 1).

Experimental

All the melting points were recorded by open capillary method and are uncorrected. Elemental analyses were performed on Perkin Elmer elemental auto analyzer. IR spectra were recorded on a Perkin Elmer RX-I FT IR spectrometer. ^{1}H NMR spectra were recorded on Bruker Advance II FT at 400 MHz spectrometer using TMS as internal standard.

Synthesis of 5-arylidenyl 2,4-thiazolidinedione (2a–g): (General procedure)

A mixture of 2,4-thiazolidinedione (0.01 mol) and aromatic aldehyde (0.01 mol) in PEG-300 (5 ml) was heated on an oil bath for 3 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mass was cooled and then poured on cold water. The obtained solid product was filtered and washed with water and then the crude was crystallized from ethanol. The purity of the product was checked by TLC. The aqueous filtrate was distilled at 100°C to remove water and thus separated PEG-300 was reused.

Selected data for compounds

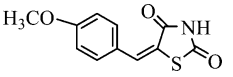
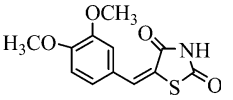
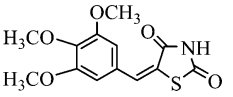
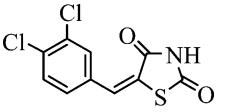
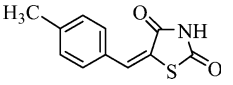
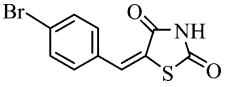
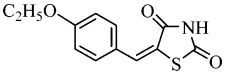
***2a**: 5-(4′-Methoxy-benzylidenyl)-2,4-thiazolidiendione*

IR (KBr, cm^{-1}): 3632 (NH symmetric stretching), 3105 (CH aromatic stretching), 2876 (CH stretching, vinylic), 2912 and 2768 (CH aliphatic asymmetric and symmetric stretching, respectively), 1729 and 1654 (C = O stretchings), 1565 (C = C stretching), 1325 (C–N stretching), 1267 (C–O–C stretching) and 764 (C–S–C stretching); ^{1}H NMR ($CDCl_3 + DMSO d_6$): 3.79 (s, 3H, OCH_3), 6.88 (d, $J = 8.2$ Hz, 2H, aromatic protons,), 7.04 (m, $J = 8.2$ Hz, 4H, aromatic protons), 7.65 (s, 1H, CH, vinylic) and 11.65 (s, 1H, NH).

***2b**: 5-(3′, 4′-Dimethoxy-benzylidenyl)-2,4-thiazolidiendione*

IR (KBr, cm^{-1}): 3650 (NH symmetric stretching), 3110 (CH aromatic stretching), 3006 (CH stretching, vinylic), 2930 and 2781 (CH aliphatic asymmetric and symmetric stretching, respectively), 1737 and 1687 (C = O stretchings), 1580 (C = C stretching), 1330

Table 1. 5-Arylidenyl-2,4-thiazolidinediones (**2a–g**).

Sr. No.	Product	Time (h)	Yield (%)	*N* (%)		*S* (%)	
				Found	Calcd	Found	Calcd
2a		3	82	5.80	5.96	13.73	13.62
2b		3	77	5.08	5.29	12.01	12.08
2c		3	78	4.65	4.74	10.70	10.85
2d		3	81	4.99	5.11	11.57	11.68
2e		3	75	6.29	6.40	14.62	14.62
2f		3	79	4.81	4.95	11.23	11.31
2g		3	84	5.49	5.63	12.91	12.86

(C–N stretching), 1272 (C–O–C stretching) and 769 (C–S–C stretching); ^{1}H NMR ($CDCl_3 + DMSOd_6$): 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.95 (d, $J =$ 2.9 Hz, 1H, aromatic protons), 7.08 (dd, $J = 2.9$ and 8.2 Hz, 1H, aromatic protons), 7.13 (d, $J = 8.2$ Hz, 1H, aromatic protons), 7.71 (s, 1H, CH, vinylic) and 11.90 (s, 1H, NH).

***2c**: 5-(3′, 4′, 5′-Trimethoxy-benzylidenyl)-2,4-thiazolidiendione*

IR (KBr, cm^{-1}): 3668 (NH symmetric stretching), 3121 (CH aromatic stretching), 3012 (CH stretching, vinylic), 2936 and 2790 (CH aliphatic asymmetric and symmetric stretching, respectively), 1734 and 1659 (C = O stretchings), 1571 (C = C stretching), 1333 (C–N stretching), 1276 (C–O–C stretching) and 766 (C–S–C stretching); ^{1}H NMR ($CDCl_3 + DMSOd_6$): 3.95 (s, 3H, OCH_3), 3.98 (s, 6H, two OCH_3), 7.05–7.09 (s, 2H, aromatic protons), 7.81 (s, 1H, CH, vinylic) and 11.93 (s, 1H, NH).

***2d**: 5-(3′, 4′-Dichloro-benzylidenyl)-2,4-thiazolidiendione*

IR (KBr, cm^{-1}): 3645 (NH symmetric stretching), 3120 (CH aromatic stretching), 3002 (CH stretching, vinylic), 2925 and 2785 (CH aliphatic asymmetric and symmetric stretching, respectively), 1735 and 1682 (C = O stretchings), 1587 (C = C stretching), 1331 (C–N stretching), 1270 (C–O–C stretching), 834 (C–Cl stretching) and 769 (C–S–C stretching); ^{1}H NMR ($CDCl_3 + DMSOd_6$): 7.10 (d, $J = 3.1$ Hz, 1H, aromatic protons), 7.35 (dd, $J = 3.1$ and 8.4 Hz, 1H, aromatic protons), 7.56 (d, $J = 8.4$ Hz, 1H, aromatic protons), 7.82 (s, 1H, CH, vinylic) and 11.98 (s, 1H, NH).

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