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Microwave-assisted efficient synthesis of spiro-fused heterocycles under solvent-free conditions

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Abstract—Spiro-fused heterocycles were synthesized in good to high yields by a pseudo four-component reaction of an aldehyde, urea and a cyclic β-diester or a β-diamide such as Meldrum's acid or barbituric acid derivatives using microwave irradiation under solvent-free conditions.

1. Introduction

The classic version of the Biginelli[1] three-component condensation reactions, which combines an aldehyde, urea or thiourea and an open-chain β-dicarbonyl compound under acidic conditions in ethanol to give a 3,4-dihydropyrimidin-2(1*H*)-one, has come into widespread use for generating large collections of molecules in combinatorial synthesis.[2] In typical procedures, the catalyst is varied under conventional heating,[3–7] microwave[8–11] and ultrasonic[12,13] irradiation in a variety of solvents and under solvent-free conditions.

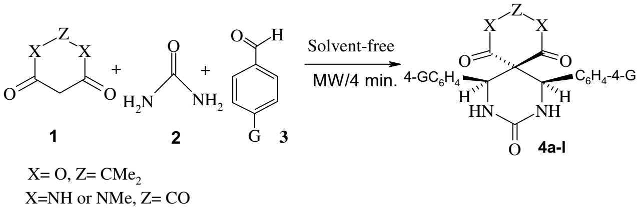
Very recently, for novel Biginelli-like scaffold synthesis, the use of the common open-chain β-dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β-diketones,[14] β-ketolactones,[15] cyclic β-diesters[16] or β-diamides,[16,17] benzocyclic ketones[18] and α-keto acids.[18] All of these reactions were performed using conventional heating and reaction times were long.

Microwave-promoted solvent-free heterogeneous reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products and manipulative simplicity.[19]

In connection with our previous work on Biginelli and Biginelli-like reactions,[16,20] we wish to report the results obtained from a study of the reaction of aldehydes, urea and Meldrum's acid or barbituric acid derivatives as a CH-acid, instead of open-chain cyclic β-dicarbonyl compounds, using microwave irradiation under solvent-free conditions. The procedure not only gives products in good yields, but avoids problems connected with solvent use (cost, handling, safety and pollution), and moreover, the reaction times are reduced from several hours to a few minutes.

2. Results and discussion

This solvent-free one-pot method involves the microwave irradiation of a mixture of Meldrum's acid or barbituric acid derivatives **1**, 1 equiv of urea **2** and 2 equiv of an aldehyde **3** in the presence of a protic acid catalyst to give, stereoselectively, a family of novel heterobicyclic compounds **4** in good yields. The stereochemistry was confirmed by the observation of three and four different signals for the three and four carbonyl groups of compounds **4a–d** and **4e–l** in the proton decoupled ^{13}C NMR spectra (Scheme 1).



Scheme 1.

Keywords: Solvent free; Multicomponent; Microwave; Biginelli reaction; Spiro-fused heterocyclic rings; Meldrum's acid; Barbituric acid.

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Table 1

4	X–Z–X	G	Yield (%)[a]			Irradiation power	Melting point (°C)
			I[b]	II[c]	III[d]		
a	O–C(Me)$_2$–O	H	51	60	73	Medium	223–225 dec
b	O–C(Me)$_2$–O	Me	48	61	70	Medium	199–200 dec
c	O–C(Me)$_2$–O	Cl	54	63	74	Medium	204–205 dec
d	O–C(Me)$_2$–O	F	52	64	72	Medium	216–218 dec
e	HN–CO–NH	H	61	70	83	Medium high	241–242 dec
f	HN–CO–NH	Me	59	71	81	Medium high	246–248 dec
g	HN–CO–NH	Cl	63	75	82	Medium high	289–291 dec
h	HN–CO–NH	F	62	73	79	Medium high	215–217 dec
i	MeN–CO–NMe	H	61	72	82	Medium high	231–232 dec
j	MeN–CO–NMe	Me	63	70	80	Medium high	227–229 dec
k	MeN–CO–NMe	Cl	64	75	81	Medium high	271–273 dec
l	MeN–CO–NMe	F	59	74	83	Medium high	243–245 dec

[a] Isolated yield.

[b] In the absence of catalyst.

[c] In the presence of NaHSO$_4$.

[d] In the presence of HOAc (reaction time 4 min).

Table 2. Pseudo four-component reaction of benzaldehyde, urea and 1,3-dimethylbarbituric acid in the presence of 1 mmol of different catalysts[a]

Entry	Catalyst	Yield (%)
1	CH_3CO_2H	82
2	CF_3CO_2H	68
3	HCl	69
4	NH_4Cl	68
5	$NaHSO_4$	72
6	4-$MeC_6H_4SO_3H$	64
7	$FeCl_3$	60
8	$ZnCl_2$	58
9	$LiClO_4$	63
10	LiBr	59
11	None	61

[a] Benzaldehyde (3 mmol), urea (1 mmol), 1,3-dimethylbarbituric acid (1 mmol), microwave irradiation.

In order to find the best catalyst for the formation of the spiro-fused compounds, the reaction of 1,3-dimethylbarbituric acid, urea and benzaldehyde was performed in the presence of various protic liquid or solid acids and Lewis acids. As indicated in Table 2, the best yields were obtained in the presence of acetic acid or NaHSO$_4$.

We repeated the syntheses of **4a–l** in the presence of acetic acid and NaHSO$_4$. The products were obtained in relatively good yields in the presence of NaHSO$_4$, but when the reactions were carried out in the presence of acetic acid the yields were increased by about 6–13% relative to using NaHSO$_4$. We also repeated the reactions in the absence of catalyst and obtained 48–63% yields with the same reaction times (see Table 1).

To explore the scope and limitations of this reaction further, we extended the procedure to various *para*-substituted benzaldehydes in the presence of Meldrum's acid and barbituric acid (Scheme 1). We found that the reaction proceeds very efficiently with benzaldehyde and electron-withdrawing *para*-substituted benzaldehydes (X = Cl, F), but only proceeded as far as the Knoevenagel adducts, when electron-releasing *para*-substituted benzaldehydes were used (X = OMe, NMe$_2$).

In conclusion, we have found that the reaction of strong CH-acids, such as Meldrum's acid or barbituric acid derivatives, with urea and aldehydes lead to an efficient synthesis of symmetrical spiro heterobicyclic compounds in high yields within short reaction times under microwave-assisted solvent-free conditions.

3. Typical procedure: synthesis of 3,3-dimethyl-(75, 11R)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]-undecane-1,5,9-trione using microwave irradiation under solvent-free conditions

A mixture of benzaldehyde (0.32 g, 3 mmol), Meldrum's acid (0.144 g, 1 mmol), urea (0.06 g, 1 mmol) and acetic acid (0.06 g, 1 mmol) were finely mixed together. The reaction mixture was placed in a screw-capped vial and irradiated for 4 min in a domestic microwave oven at medium power. After cooling, the reaction mixture was poured onto crushed ice (40 g) and stirred for 5–10 min. The separated solid was filtered under suction, washed with cold water (40 mL) and then recrystallized from ethyl acetate/*n*-hexane (1:3) to afford the pure product **4a**. White powder (0.28 g, 73%). Mp 223–225 °C dec. IR (KBr) (ν_{max}, cm^{-1}): 3193 and 3061 (NH), 1771, 1732 and 1687 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6, Me$_4$Si): δ_H 0.50 (6H, s, CMe$_2$), 5.30 (2H, s, 2CH), 7.21–7.37 (10H, m, Ar), 7.28 (2H, s, 2NH). ^{13}C NMR (125 MHz, DMSO-d_6, Me$_4$Si): δ_C 27.66 (C*Me*$_2$), 57.98 (C$_{spiro}$), 61.49 (2CH), 105.51 (*C*Me$_2$), 127.73, 128.70, 129.26 and 135.55 (Ar), 155.20, 159.66, 165.56 (3C=O), MS (EI, 70 eV) (*m*/*z*, %) 380 (M$^+$, 11), 322 (7), 294 (13), 234 (12), 175 (17), 106 (100), 77 (44), 43 (56).

3.1. 4e: (7*S*,11*R*)-Diphenyl-2,4,8,10-tetraazaspiro[5.5] undecane-1,3,5,9-tetraone

White powder. Mp 241–242 °C dec. IR (KBr) (ν_{max}, cm^{-1}): 3240 and 3065 (NH), 1729 and 1695 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6, Me$_4$Si): δ_H 5.21 (2H, s, 2CH), 7.17–7.31 (10H, m, Ar), 7.31 (2H, s, 2NH), 11.01 and 11.39 (2H, 2s, NH). ^{13}C NMR (125 MHz, DMSO-d_6, Me_4Si): δ_C 57.49 (C_{spiro}), 61.59 (2CH), 127.81, 128.91, 129.36 and 136.12 (Ar), 149.11, 156.05, 165.88 and 170.31 (4C=O). MS (EI, 70 eV) (*m*/*z*, %) 364 (M^+, 5), 304 (10), 215 (95), 104 (100), 77 (96), 51 (98).

3.2. 4i: 2,4-Dimethyl-(7*S*,11*R*)-diphenyl-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9 tetraone

White powder. Mp 231–232 °C dec. IR (KBr) (ν_{max}, cm^{-1}): 3180 and 3060 (NH), 1739 and 1685 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6, Me_4Si): δ_H 2.68 and 2.85 (6H, s, 2NMe), 5.28 (2H, s, 2CH), 7.08–7.28 (10 H, m, Ar), 7.18 (2H, s, 2NH). ^{13}C NMR (125 MHz, DMSO-d_6, Me_4Si): δ_C 27.87 and 28.71 (2NMe), 58.83 (C_{spiro}), 62.04 (2CH), 127.43, 128.84, 129.49 and 135.93 (Ar), 149.44, 155.87, 163.67 and 168.27 (4C=O). MS (EI, 70 eV) (*m*/*z*, %) 392 (M^+, 17), 260 (13), 243 (31), 186 (18), 106 (100), 77 (39), 51 (33).

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