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Microwave Induced One Pot Synthesis of Dihydropyrimidine Based on Furochromone

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Abstract: Dihydropyrimidines were synthesized by using a microwave radiation of formylfurochromone, urea derivatives and β-ketoesters. Different reaction media have been carried out to optimize the best reaction condition to obtain the highest yield. All products were isolated, purified and identified by analytical and spectroscopic data.

Keywords: Microwave, dihydropyrimidine, Bignilli type reaction.

Introduction

Recently, the preparation of fine chemicals following environmentally friendly strategies represents a challenging goal in the field of synthetic organic chemistry[1-3]. Dihydroprimidines (DHMPs) have found remark-able pharmacological efficiencies[4-8], such as antiviral, potent Ca-Channel blockers, antihypertensive and anti-tumer. In addition, Furobenzo-pyranes play an important role as pharmaceuticals[9-12]. The Biginilli type reaction, first describ more than a century ago[13] and recently reviewed[14]. In this paper, in continuation of our interests[15,19] on the synthesis of heterocyclic derivatives we aim to study the effect of the rapid heating cabability of a microwave oven among various acid or base catalysts on the synthesis of DHMPs.

Experimental

All melting points were determined on a Gallenkamp apparatus were uncorrected. The IR spectra were recorded in KBr disks, on a Jasco Fourier Transfonn Infrared Spectrophotometer Model FT/IR3000E. The ^{1}HNMR were recorded (DMSO-*d6*,) on JOEL JNM-EX 270 FTNMR system (NRC) and chemical shifts are recorded in ppm relative to TMS. The MS were performed at 70 e V on a Finnigan MAT SSQ 7000 spectrometer. The microanalysis were carried out at the microanalytical Center, Cairo University, Egypt. The results of elemental analysis for C and H were satisfactory within the range ±0.4%. All solvents were purified and dried. Urea derivatives and active methylene compounds were commercially available and purchased from Fluka.

Preparation of DHPMs 6a-f, 9 and 10:

Method A:

1) *in absence of microwave radiation:*

To a mixture of an aldehyde **1** (10 mmol), (thio)urea **2** (0.76 g, 10 mmol), active methylene compounds **3a-c** and / or **8** (1.0 ml, 10 mmol) and piperidine (2.0 ml, 20 mmol) in absolute ethanol (50 ml) was heated under reflux for an appropriate period (8-10 h). After cooling to room temperature, The resultant soild was dissolved in water (6 ml) and the solution was neutralized by slow addition of 2N HCI that caused crystallization to give adduct **6**a-f.

2) *Under the influence of microwave*

Similarly, as mention above, but the mixture was subjected to microwave radiation for pro per time (3-5 min).

Method B:

A mixture of **1** (1.0 mol), (thio)urea **2** (1.5 mol) and active methylene compounds **3**a-c and / or **8** (1.1 mol) and dry acetic acid (0.4 mol) was mixed in a pyrex test tube and subjected to microwave irradiation for proper time (3 min). after cooling to room temperature, the solid mass was washed with water, filtered and dried in vacuum to afford pure product.

Method C:

Similarly, the three component **1**,**2**,**3** and / or **8** were mixed together in presence of silica gel in a Pyrex tube which placed in an alumna bath and subjected to microwave radiation for (3-4 min). After cooling to room temperature, The products eluted with methanol which evaporated under reduced pressure and purified by column chromatography as mentioned above and recrystallized from appropriate solvent.

5-acetyl-4-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 6a: yield 70-82%, m.p. 170-72 ºC (ethanol); IR (KBr): 3222, 3125 cm^{-1} (NH), 1697, 1660, 1618 cm^{-1} (3C= O). ^1H NMR (DMSO-d-6): δ_{ppm}= 9.26 (1H, s, NH exchangeable D_2O), 7.51, 6.66 (2H, dd, H-2, H-3, J = 2.5 Hz), 7.78 (1H, s, H-7), 7.24 (1H, s, NH exchangeable D_2O), 5.01 (1H, s, H-4); 4.16, 4.09 (6H, 2s, $2OCH_3$); 1.81 (3H, s, CH_3). MS for $C_{20}H_{20}N_2O_7$ (400.38): m/z: (%) = 400 (50), 367 (26), 355 (79), 312 (55), 205 (100).

6-(5-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-4,9-dimethoxy-5*H*-furo[3,2-*g*]chromen-5-one6b: yield 55-60%, m.p. 235-6 ºC (ethanol); IR (KBr): 3360, 3300 cm^{-1} (NH), 1687, 1620 (2C= O), 1050 (C = S). ^1H NMR (DMSO-d-6): δ_{ppm}= 9.07 (1H, s, NH exchangeable D_2O), 7.60, 6.66 (2H, dd, H-2, H-3, J = 2.00 Hz), 7.70 (1H, s, H-7), 7.40 1H, (s,NH, exchangeable D_2O), 5.46 (1H, s, H-4), 4.08, 4.08 (6H, 2s, $2OCH_3$), 2.34 (3H, s, $COCH_3$), 1.80 (3H, s, CH_3). MS for $C_{20}H_{19}N_2O_6S$ (415.44): m/z: (%) = 414(69), 371 (89), 341 (39), 312 (43), 282 (41), 177 (100).

Ethyl1,2,3,4-tetrahydro-4-(4,9-dimethoxy-5-oxo-5*H*-furo-[3,2-g]chromen-6-yl)-6-methyl-2-oxo -pyrimidine-5-carboxylate) 6c: yield 56- 61, m.p. 213-5 ºC (ethanol), IR (KBr): 3322, 3214 cm^{-1} (NH), 1740 ,1998, 162O cm^{-1} (3C=O). ^1H NMR (DMSO-d-6): δ_{ppm}= 9.30,8.13(2H, ss, 2NH exchangeable D_2O), 7.51, 6.63 (2H,dd,H-2 ,H-3, J=2.4 H_Z), 7.42 (1H,s,H-7), 6.50 1H, (s,NH, exchangeable D_2O), 5.23(1H,s,H-4), 4.21, 4.00 (6H, dd, $2OCH_3$), 4.03-3.90 (2H,q,CH_2 ester), 2.22 (3H, s, CH_3), 1.10 (3H, t, CH_3 ester). MS for $C_{21}H_{20}N_2O_8$ (428.39): m/z % = 428 (87), 355 (100), 311(38), 246 (80).

Ethyl-1,2,3,4-tetrahydro-4-(4,9-dimethoxy-5-oxo-5*H*-furo-[3,2-g]chromen-6-yl)-6-methyl-2-thi oxopyrimidine-5-carboxylate) 6d: yield 33-36%, m.p. 205-6 (ethanol), IR(KBr):3140, 3120 cm^{-1} (NH), 1690 ,1620 cm^{-1} (2C=O) , 1060 cm^{-1} (C=S). ^1H NMR(DMSO-d-6):δ_{ppm}= 9.30,8.01(2H, ss, 2NH exchangeable D_2O), 7.90, 7.04 (2H,dd,H-2 ,H-3, J=2 H_Z), 7.95 (1H,s,H-7), 6.40 1H, (s,NH, exchangeable D_2O), 5.25(1H,s,H-4), 4.10, 3.88 (6H,dd,$2OCH_3$), 3.91-3.83 (2H,q,CH_2 ester), 2.31(3H,s,CH_3), 1.60 (3H,t,CH_3 ester). MS for $C_{21}H_{20}N_2O_7S$ (444.46): m/z %= 444(70), 371(100), 311(47).

(Tert-butyl-1,2,3,4-tetrahydro-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]-chromen-6-yl)-6-methyl -2-oxopyrimidine-5-carboxylate) 6e: yield 22-28 %, m.p. 245-7 ºC (ethanol), IR (KBr): 3220, 3120 cm^{-1}(NH); 1700, 1680, 1620 cm^{-1} (3C= O). ^1H NMR (DMSO-d-6), δ_{ppm}= 9.09 (1H, s, NH exchangeable with D_2O), 7.66, 6.60 (2H, dd, H-2, H-3, J = 2.10 Hz), 7.55 (1H, s, H-7), 6.10 (1H, s, NH exchangeable D_2O), 5.31 (1H, s, H-4), 4.19, 4.03 (6H, 2s, $2OCH_3$), 1.7.51 (3H, s, CH_3), 1.40 (9H, s, 3 CH_3). MS for $C_{23}H_{24}N_2O_8$ (456.45): m/z (%) = 456 (100); 425 (50); 414 (69), 399 (81), 355 (40), 312 (55) 281 (41), 205 (57), 177 (70).

(Tert-butyl1,2,3,4-tetrahydro-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]-chromen-6-yl)-6-methyl-2-thioxopyrimidine-5-carboxylate) 6f: yield 20-25%, m.p. 203-5 ºC (ethanol), IR (KBr): 3219, 3110 cm^{-1} (NH), 1670, 1622 cm^{-1} (3C= O), 1059 cm^{-1} (C = S). ^1H NMR (DMSO-d-6), δ_{ppm}= 10.55, 9.80 (1H, s, NH exchangeable with D_2O), 7.71, 6.61 (2H, dd,H-2, H-3, J = 2.00 Hz), 7.52 (1H, s, H-7), 6.07 (1H, s, NH exchangeable with D_2O), 3.15 (1H, s, H-4), 4.00, 3.91 (6H, 2s, $2OCH_3$), 2.12 (3H, s, $COCH_3$), 1.25 (9H, s, $3CH_3$). MS for $C_{23}H_{24}N_2O_7S$ (472): m/z (%) = 472 (90), 441 (80), 427 (85), 397 (40),384(20), 346 (100), 313 (40), 244 (20), 220 (45), 205 (70).

(Hexahydro-4-(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-g]chromen-6-yl)-2,6-dioxopyrimidine-5-carbonitrile) 9a: yield 46-57%; m.p. 198-200 ºC (ethanol), IR (KBr): 1798, 1646, 1627 cm^{-1} (3C= O), 2200 cm^{-1} (CN). ^1H NMR (DMSO-d-6): δ_{ppm}= 9.27 (1H, s, NH exchangeable D_2O), 7.68, 6.61 (2H, dd, H-2, H-3, J = 2.1 Hz), 7.53 (1H, s, H-7), 6.22 (1H, s, NH exchangeable D_2O), 4.16, 4.09 (6H, 2s, $2OCH_3$). MS for $C_{18}H_{13}N_3O_7$ (383.31): m/z (%) = 383 (61), 371 (2), 340 (7), 314 (12), 283 (7), 220 (78), 205 (84).

(Hexahydro-4-(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-g]chromen-6-yl)-6-oxo-2-thioxopyrimidine-5-carbonitrile) 9b: yield 35-44%; m.p. 228-30 ºC (acetone). IR (KBr): 1688, 1626 cm^{-1} (2C= O), 2200 cm^{-1} (CN), 1050 cm^{-1} (C = S). ^1H NMR (DMSO-d-6), δ_{ppm}= 9.62 (1H, s, 1NH exchangeable with D_2O), 7.66, 6.66 (2H, dd, H-2, H-3, J = 2.1 Hz), 7.66 (1H, s, H-7), 6.01 (1H, s, 1NH exchangeable with D_2O), 4.10, 3.81 (6H, 2s, $2OCH_3$). MS for $C_{18}H_{13}N_3O_6S$ (399.38): m/z (%) = 399(100), 386 (55), 255 (31), 220 (92), 205 (50), 191 (33).

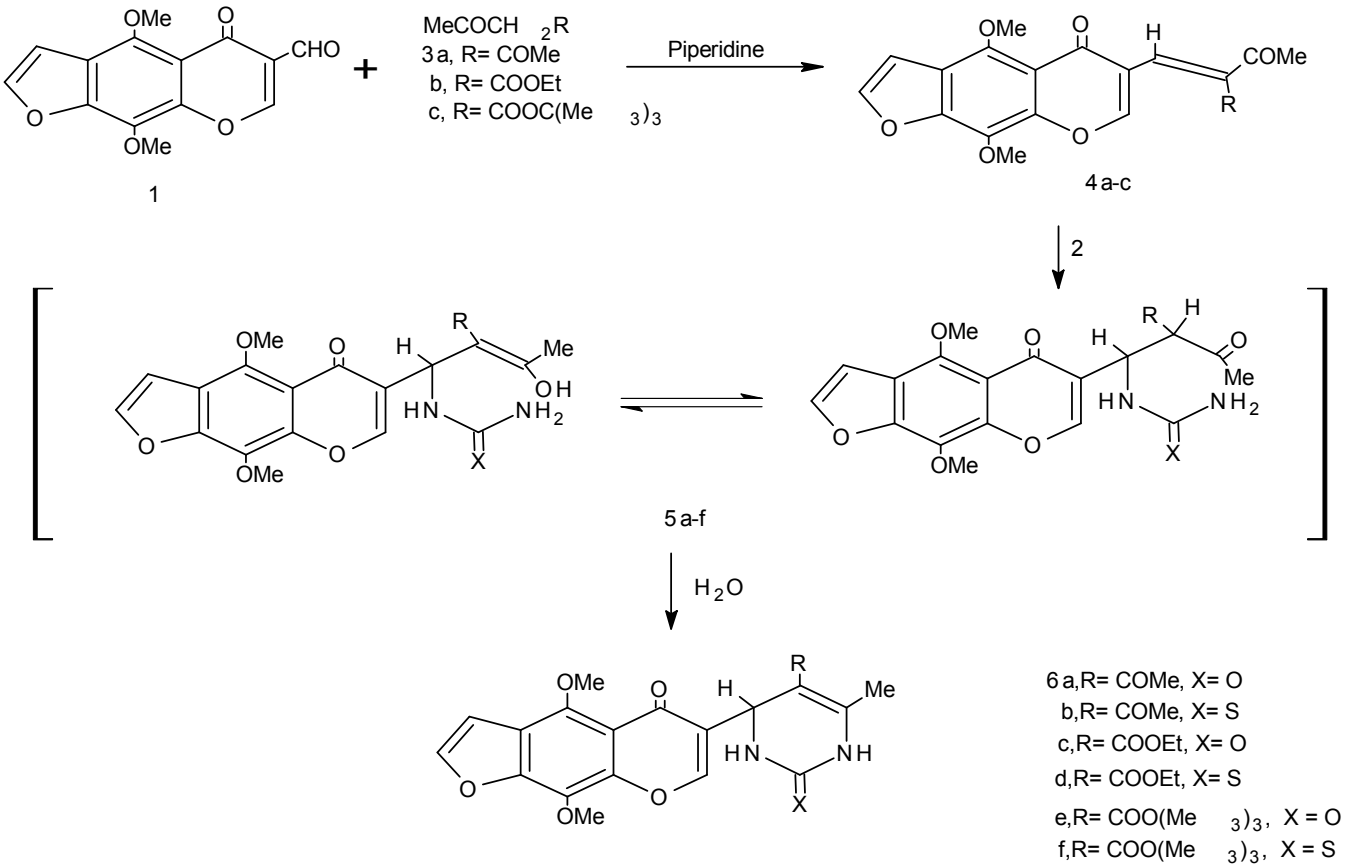
(Ethyl4-amino-1,25,6-tetrahydro-6-(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-g]-chromen-6-yl)-2-oxopyrimidine -5-carboxylate) 10a: yield 52-66%; m.p. 192-4 ºC (ethanol). IR (KBr): 3401-3375 cm^{-1} (NH_2); 3128 cm^{-1} (NH), 1698, 1660, 1627 cm^{-1} (3C= O). ^{1}HNMR (DMSO-d-6), δ 9.27 (1H, s, NH exchangeable D_2O), 7.72, 6.61 (2H, dd, H-2, H-3, J = 2.1 Hz), 4.30 (2H, q, CH_2-ester), 3.90, 3.80 (6H, 2s, $2OCH_3$), 2.15 (2H, br, NH_2 exchangeable with D_2O), 1.29, (3H, t, CH_3-ester). MS for $C_{20}H_{17}N_3O_8$ (427): m/z (%) = 426 (88), 398 (54), 367 (26); 355 (79), 312 (55), 205 (60).

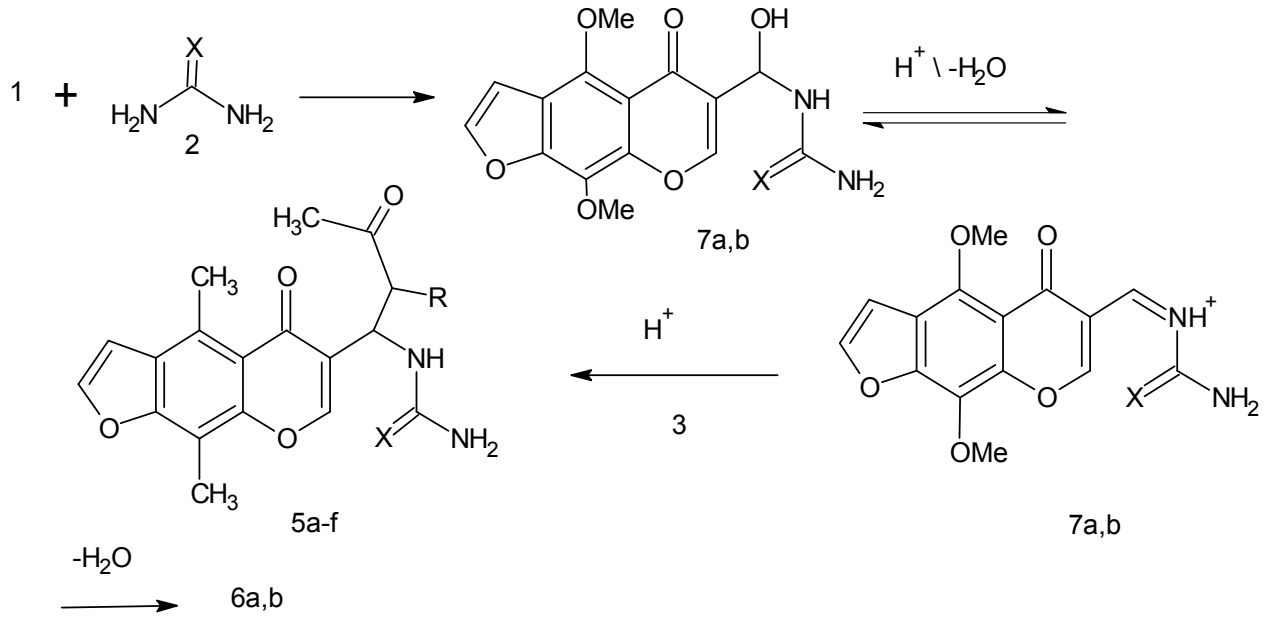
(Ethyl-4-amino-1,2,5,6-tetrahydro-6-(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-g]-chromen-6-yl)-2-thioxopyrimidine-5-carboxylate) 10b: yield 50-55%; m.p. 203-5 ºC (ethanol), IR (KBr): 3360, 3300 cm^{-1} (NH_2), 3210 cm^{-1} (NH), 1698, 1620 cm^{-1} (2C= O), 1050 cm^{-1} (C = S). ^{1}H NMR (DMSO-d-6): δ_{ppm}= 10.20 (H, s, NH exchangeable with D_2O), 7.61, 6.64 (2H, dd, H-2, H-3, J = 2.1 Hz), 7.43 (1H, s, H-7), 4.42 (2H, q, CH_2-ester), 3.92, 3.83 (6H, 2s, $2OCH_3$), 2.23 (2H, br, NH_2 exchangeable with D_2O); 1.31 (3H, t, CH_3-ester). MS for $C_{20}H_{19}N_3O_7S$ (445.45): m/z (%) = 445(21), 443 (86), 434 (40), 421 (42), 406 (20), 393 (23), 246 (30), 191 (10).

Results and Discussion

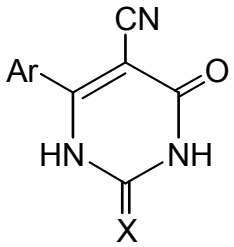
This method employed a one-pot three-component condensation. Thus, 4,9-dimethoxy-5-oxo-furo-[3,2-g]benzopyran-6-carboxyaldehyde **1** reacted with β-diketones namely, acetyl acetone (**3a**), ethyl acetoacetate **3b** and tert-butylacetoacetate **3c** and (thio)urea **2** in ethanol in presence of piperidine as a base under the influence or absence of microwave radiation. The mechanism of this reaction was taken place via the knoevenagel condensation of aldehyde **1** and active methylene compound **3** to afford the benzylidine **4** as intermediate, In the presence of piperidine, (thio)urea **2** attacked the olefinic double bond, followed by lossed of water as a result of the formation of the enol form **5** to give the dihydropyrimidins **6a-f** (scheme 1)[20-22]. The structure of the obtained compounds were confirmed by their analytical and spectroscopic data (*cf.* Experimental).

Scheme 1

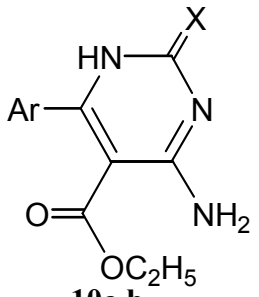




Scheme 2



9a,b



10a,b

On subjecting the typical Biginelli reaction (EtOH/HCI)[15] of the three-component condensation reaction of **1**, **2** and **3** to microwave radiation, the same products **6a-f** have been obtained in better yield than those obtained from the previously reactions. We extended our research by running the reaction of **1** with (thio)urea **2** and β-ketoester **3** in dry acetic acid as a catalyze in the reaction medium under microwave radiation. We obtained the DHPMs **6a-f** in good yields and very pure comparing with products that obtained from running the reaction in Ethanol / HCI or ethanol / piperidine as previously mentioned. This may be due to the high polarity of acetic acid which coupled effectively with microwave radiation and generated heat energy required to promote the reaction. The rate enhancement under microwave irradiation may be attributed to the effective absorption of microwave irradiation by the polar media[23]. The first step in this mechanism involved the acid-catalyzed formation of an N-acyliminium ion precursor of type **7** from an aldehyde and (thio)urea components. The second step can be regarded as an addition of π-nucleophile, i.e. the enol tautomer 1,3-dicarbonyl compounds **1** to the electron deficient N-acylimium species **7** yielding dihydropyrimidines of type **6** (scheme 2)[24] . In order to be able to carry out such Biginilli condensation, in a faster and more efficient way without using solvent. We investigated the influence of microwave irradiation on a neat mixture of aldehyde **1,** (thio)urea derivative **2** and ketoester **3** with or without silica gel as a solid support. After some experiments with respect to molar ratio of reagents, irradiation time, and power of the microwave set-up, we have found a set of conditions that generally provides DHPMs in excellent yields. These conditions employed a 1.1: 1.0: 1.50 ratio of β-ketoester, aldehyde and (thio)urea respectively, using silicagel as solid support and catalyst.

In a typical experiment, the three reaction components were mixed and supported on silicagel in glass beaker and exposed to microwave irradiation for suitable time.

The purity of the crude product was lowered and purification by chromatography or crystallization had to be carried out. These results promoted us to extended the scope of this microwave mediated Bignilli procedure and have carried out the synthesis of DHPMs analogue **9a,b** by reacting the aldehyde, thiourea and ethylcyanoacetate **8** as an example of non enol form of active methylene compounds in the presence of pipiredine as a catalyst. Unexpectedly, **10a,b** was formed from running the three-component reaction **1**, **2**, and **8** in solventless reactions using silicagel as a catalyst. Structure of **10a,b** was confirmed by its ^{1}H NMR. On the other hand, IR of compounds **10a,b** show a peak at 1698cm^{-1} for (C=O ,ester group), in addition to the disappearance of the CN group. Furthermore, on running this reaction in liquid phase, such as ethanol / HCI or dry acetic acid as medium and catalyst, the same product **9** was isolated (comparative TLC, IR and mixed melting points).

Conclusion: In a conclusion, on running the reaction under the influence of microwave radiation, the yield of DHPMs obtained by using of acid as a catalyst is higher than using of piperidine. The purest compounds were obtained on running the reaction in dry acetic acid. On the other hand, two different products were obtained in case of ethylacyanoacetate depend on the reaction medium. Thus, microwave radiation has been applied to accelerate reaction rates and to improve the yields of the products.

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