Heteroatom Chemistry
Volume 18, Number 6, 2007

One-Pot Synthesis of Novel Substituted Pyrrolo[2,3-*d*]pyrimidines Using Dry Media

M. Kidwai, K. Singhal, and S. Kukreja

Green Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

Received 7 February 2006; revised 12 August 2006

ABSTRACT: *A convenient solvent-free one-pot synthesis of 1,3,5,7-tetraaryl-1,3,4,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one derivatives using supported reagents under microwave irradiation is described.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:617–621, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20355

INTRODUCTION

Industries in the new millennium have widely accepted the concept of "green chemistry" to meet the fundamental challenges of environmental protection. One of the thrust areas for achieving this target is the use of microwaves [1,2] not only as an alternative energy source but also as a technique to substantially increase yield and reduce reaction time. The solid supports are usually of mineral origin and act both as catalyst [3] and an energy transfer medium. These are used to carry out reactions in open vessels, avoiding the risk of high-pressure development, with the possibility of upscaling the reactions to industrial level [4].

The pyrrole heterocycle is a very attractive target in heterocyclic and combinatorial chemistry, as it is a motif in many bioactive natural products [5]. Also pyrimidines have been studied for more than a century because of their wide-ranging pharmaceutical applications as antimicrobial, antitumor, antihypertensive [6], and anti-inflammatory agents. The pyrrolo-fused pyrimidines further represent an important class of compounds being the constituent unit of nucleobases. Pyrrolo[2,3-*d*]pyrimidinones reveal significant biological profiles as broad-spectrum antitumors [7], antibacterials, antivirals, inhibitory activity against dihydrofolate reductase (DHFR) and thymidylate synthase enzymes with CNS and immunosuppressive activities [8]. Moreover, this efficient assembly is also significant importance in synthetic chemistry.

Although few methods have been exemplified in the literature for the synthesis of pyrrolo[2,3-*d*]pyrimidinones, starting from uracil or dimethyl acetal of uracils [9], but most of them involve multistep synthetic reactions including the formation of intermediates using undesirable harmful chemicals and catalysts with a major disadvantage of requiring severe conditions in steps like cyclization. So, there is need for simple, efficient, and more general method to synthesize such heterocyclic moieties. Notably, the coupling of three components in a single flask under MWs can be proved as an alternative and more direct strategy to afford pyrrolo[2,3-*d*]pyrimidinone core. This single flask approach avoids the use of any type of catalysts that may contaminate final compounds, employs readily available materials, and has the potential to directly install diverse elements around the basic pyrrolo[2,3-*d*]pyrimidinone skeleton.

Moreover, no general method for the synthesis of titled compound pyrrolo[2,3-*d*] pyrimidinones using nitroalkanes, amines, and chalcones has ever been reported.

Correspondence to: M. Kidwai; e-mail: kidwai.chemistry@gmail.com.

Contract grant sponsor: Council of Scientific and Industrial Research (CSIR), New Delhi, India.

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In view of the diverse therapeutic activity of pyrrolo[2,3-*d*]pyrimidinones and our ongoing endeavor [10] to develop new selective and environmentally benign methodologies using microwave irradiation (MWI), we herein report a one-pot method that allows a three-component coupling reaction of α,β-unsaturated ketones, amines, and nitromethane to afford pyrrolo[2,3-*d*]pyrimidinones. The prevalence of these types of three-component reactions [11] is increasingly due to their improved efficiency and atom economy with structural diversity.

RESULTS AND DISCUSSION

1,3,5,7-Tetraaryl-2-thioxo-1,3,5,7-tetrahydropyrrolo-[2,3-*d*]pyrimidine-4-ones (**4a–g**) were prepared by microwave irradiation of adsorbed three components α,β-unsaturated ketones (chalcones) (**1a–c**), aromatic/heteroaromatic amines (**2a–c**), and nitroalkanes (**3**) over neutral alumina Aluminum oxide neutral, Brockmann I (Aldrich Chem. Co., cat. no. 19, 977-4), ~150 mesh, 58 Å, surface area 155 m^2/g or basic alumina Aluminum oxide basic, Brockmann I (Aldrich Chem. Co., cat. no. 19, 944-3), ~150 mesh, 58 Å, surface area 155 m^2/g. The basic skeleton of chalcones possessing α,β-unsaturated carbonyl group has always been a useful synthon for various heterocyclic compounds of pharmacological importance. Notably, the chalcones particularly synthesized by condensation of *N*,*N*-disusbstituted 2-thiobarbituric acids (TBAs) with aromatic/heteroaromatic aldehydes react with various aromatic/heteroaromatic amines furnishing α,β-unsaturated imines that further couple with nitromethane affording cyclized products in fair to good yields by eliminating H_2O and HNO.

It has been sometimes reported that nitroethane gives better results than nitromethane [12]. But it is interesting to note that the coupling of these α,β-unsaturated imines (containing 2-thioxo-pyrimidine moiety) with nitromethane too affords the products with reasonable yields, thus sharing an advantage of high reactivity with fair efficiency.

Furthermore, Table 1 clearly highlights the versatility of various solid supports. The reaction was also tried under neat reaction conditions (without any solvent or support catalyst). But no results were obtained under neat reaction conditions, thus emphasizing the importance of solid support, which acts both as a catalyst as well as energy transfer media. Drastic reduction in the reaction time and improved yield was thus observed owing to rapid heating capability of recyclable solid supports under MWs.

For comparative studies, conventional synthesis was also performed. Reaction in the presence of basic media like pyrrolidine using oil bath did not give satisfactory results because charring occurred, whereas conventional refluxing using $AlCl_3$ as a catalyst gave the products in 18–22 h with very less yields. Furthermore, it is observed that the amount of nitromethane required in the case of synthesis using microwaves is just 2 mmol instead of 4 mmol used in the conventional heating procedure.

The structures of the synthesized compounds (**4a–g**) were established on the basis of elemental analysis and spectral data. The molecular formulae were confirmed by elemental analysis. The characteristic peaks of chalcones (α,β-unsaturated ketones) at 1665–1680 cm^{-1} and at 1530–1545 cm^{-1} were due to C=O group and C=C group of α,β-unsaturated carbonyl skeleton, respectively, and show slight shift in the products (**4a–g**).

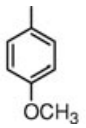
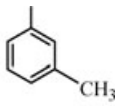
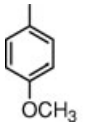
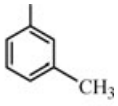
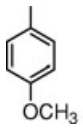
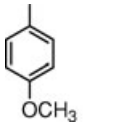
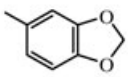
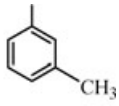
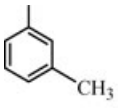
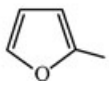
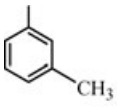
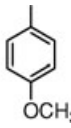
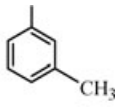
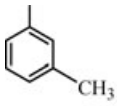
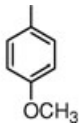
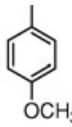
In addition, the existence of product structure (**4**) was fairly supported by the comparison of ^{1}H NMR spectra of chalcones (**1**) and products (**4**) taken in $CDCl_3$. In the ^{1}H NMR spectra of chalcone, the presence of a singlet for one proton at δ 8.2 due to —CO—C=C(H)—R′ group disappeared in the case of pyrrolo[2,3-*d*]pyrimidin-4-ones with the appearance of a singlet of 1H for C_6-H at δ 6.8, helping in the final proof characterizations of the proposed product.

In conclusion, the present paper describes a one-pot direct methodology for the synthesis of bioactive pyrrolo[2,3-*d*]pyrimidines using dry media. The use of chalcones of *N*,*N*-disusbstituted TBAs clearly highlights them as highly reactive reactants, which further prove that such a method is less time consuming with high efficiency and allows the rapid assembly of structurally diverse pyrrolo[2,3-*d*]pyrimidines. Various advantages of this multifunctional environment friendly coupling reaction include simplicity, improved product yield, and shorter reaction time as compared to the conventional reaction.

EXPERIMENTAL SECTION

Melting points were recorded a Thomas Hoover melting point apparatus and are uncorrected. IR (in nujol) was recorded on a Perkin–Elmer FTIR-1710 spectrophotometer, ^{1}H NMR spectra were recorded on a FTNMR Hitachi R-600 (60 MHz) spectrometer using TMS as internal standard. Elemental analysis was performed on a Heraeus CHN rapid analyzer. The purity of compounds was checked on silica gel coated aluminum plates (Merck). A Kenstar microwave oven, model No. OM9925E at 2450 MHz, 800 W, was used for MWI. All of these instruments

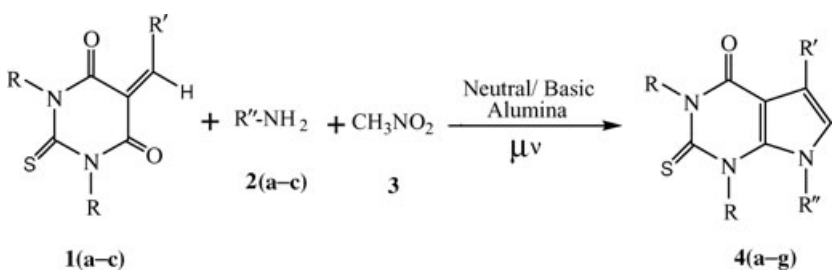
TABLE 1 Comparison of Reaction Time and Yield for the Synthesis of **4**(**a–g**)

				Method A Time (min)/Yield (%)		
Compound	*R*	*R′*	*R″*	*Basic Alumina*	*Neutral Alumina*	*Method B Time (h)/Yield (%)*
4a				4/62	4/58	17.30/30
4b				3.30/66	4/60	17/35
4c				4/60	5/60	19/28
4d				4.30/68	5/68	18.30/32
4e				5.30/60	5.30/56	20/30
4f				4/65	4.30/62	19.30/40
4g				5/68	6/65	22/34

were available at the Department of Chemistry, University of Delhi, Delhi-7, India.

General Procedure for the Synthesis of Pyrrolo-[2,3-d]pyrimidinones

Method A: Microwave Assisted Solid Supported Synthesis. To the solution of chalcones of *N*,*N*-disubstituted thiobarbituric acids (**1a–c**) (0.01 mol) and aromatic/heteroaromatic amines (**2a–c**) (0.01 mol) and nitromethane **3** (0.02 mol) in chloroform, neutral alumina or basic alumina (20 mg) was added. The reaction mixture was air-dried. This was then subjected to MWI after placing it in an alumina bath [13] at the time interval of 30 s. Upon completion of the reaction, as monitored by TLC, the reaction



SCHEME 1

mixture was cooled and product (**4a–g**) was eluted using 3 × 10 mL of chloroform (Scheme 1) and was recrystallized using an appropriate solvent.

Method B: Conventional Solution Phase Synthesis. A mixture of chalcone (**1a–c**) (0.01 mol) and aromatic/heteroaromatic amines (**2a–c**) (0.01 mol) and nitromethane **3** (0.04 mol) in chloroform was taken, and catalytic amount of $AlCl_3$ was then refluxed in oil bath. The heating was continued for approximately 18–22 h, and the reaction progress was monitored by TLC. Upon completion of the reaction, the solvent was evaporated to obtain crude product.

1,3-Diphenyl-5-(p-methoxyphenyl)-7-(m-tolyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d] pyrimidin-4-one (**4a**). Mp 110–112°C; anal. calcd for $C_{32}H_{25}N_3O_2S$: C 74.56, H 4.85, N 8.15, S 6.21%; found C 74.61, H 4.82, N 8.17, S 6.24%; IR ν (cm^{-1}): 1670 (C=C–C=O), 1600 (C=C arom), 1255 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.8 (s, 1H, C_6-H), 6.9–7.8 (m, 18H, arom).

1,3-Di(p-methoxyphenyl)-5-phenyl-7-(m-tolyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one (**4b**). Mp 125–127°C; anal. calcd for $C_{33}H_{27}N_3O_3S$: C 72.66, H 4.95, N 7.70, S 5.87%; found C 72.69, H 4.98, N 7.62, S 5.91%; IR ν (cm^{-1}): 1664 (C=C–C=O), 1605 (C=C arom), 1245 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 3.8 (s, 6H, OCH_3), 6.9 (s, 1H, C_6-H), 7.0–7.8 (m, 17H, arom).

5,7-Diphenyl-1,3-di(p-methoxyphenyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one (**4c**). Mp 114–116°C; anal. calcd for $C_{32}H_{25}N_3O_3S$: C 72.31, H 4.70, N 7.90, S 6.02%; found C 72.34, H 4.75, N 7.88, S 6.08%; IR ν (cm^{-1}): 1662 (C=C–C=O), 1600 (C=C arom), 1251 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 3.7 (s, 6H, OCH_3), 6.7 (s, 1H, C_6-H), 6.9–7.8 (m, 18H, arom).

5,-(1,3-Benzodioxol-5-yl)-1,3-di(p-methoxyphenyl)-7-(p-tolyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]-pyrimidin-4-one (**4d**). Mp 146–148°C; anal. calcd for $C_{34}H_{27}N_3O_5S$: C 69.26, H 4.58, N 7.13, S 5.43%; found C 69.38, H 4.39, N 7.12, S 5.36%; IR ν (cm^{-1}): 1664 (C=C–C=O), 1607 (C=C arom), 1247 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 3.7 (s, 6H, OCH_3), 5.9 (s, 2H, CH_2), 6.7 (s, 1H, C_6-H), 6.9–7.7 (m, 15H, arom).

5-(Furan-2-yl)-1,3-di(m-tolyl)-7-phenyl-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one (**4e**). Mp 146–148°C; anal. calcd for $C_{30}H_{23}N_3O_2S$: C 73.61, H 4.70, N 8.58, S 6.54%; found C 73.56, H 4.72, N 8.59, S 6.60%; IR ν (cm^{-1}): 1670 (C=C–C=O), 1610 (C=C arom), 1255 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.2 (s, 6H, CH_3), 6.7 (s, 1H, C_6-H), 6.8–7.8 (m, 16H, arom).

5-(p-Methoxyphenyl)-1,3,7-tri(m-tolyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one (**4f**). Mp 180–182°C; anal. calcd for $C_{34}H_{29}N_3O_2S$: C 75.13, H 5.34, N 7.73, S 5.89%; found C 75.15, H 5.29, N 7.77, S 5.81%; IR ν (cm^{-1}): 1649 (C=C–C=O), 1609 (C=C arom), 1251 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 9H, CH_3), 3.7 (s, 3H, OCH_3), 6.8 (s, 1H, C_6-H), 7.0–7.7 (m, 16H, arom).

5,7-Di(p-methoxyphenyl)-1,3-di(m-tolyl)-1,3,5,7-tetrahydro-2-thioxopyrrolo[2,3-d]pyrimidin-4-one (**4g**). Mp 140–141°C; anal. calcd for $C_{34}H_{29}N_3O_3S$: C 72.98, H 5.18, N 7.51, S 5.72%; found C 72.94, H 5.21, N 7.47, S 5.65%; IR ν (cm^{-1}): 1656 (C=C–C=O), 1607 (C=C arom), 1250 (C=S); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.2 (s, 6H, CH_3), 3.8 (s, 6H, OCH_3), 6.8 (s, 1H, C_6-H), 6.9–7.8 (m, 16H, arom).

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