N-Bromosuccinimide as an Almost Neutral Catalyst for Efficient Synthesis of Dihydropyrimidinones Under Microwave Irradiation

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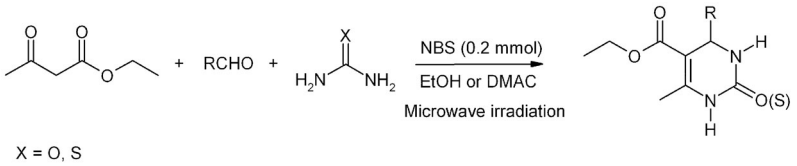
Abstract: NBS has been used as a mild, efficient and almost neutral catalyst for the preparation of dihydropyrimidinones (DHPMs) and the corresponding thio-derivatives under microwave irradiation. By this method, a wide variety of DHPMs were synthesized in good to high yields.

Key words: *N*-bromosuccinimide, dihydropyrimidinones, microwave irradiation

Dihydropyrimidinones (DHPMs) derivatives have attracted considerable interest in recent years due to their promising activities as calcium channel blockers,[1] antihypertensive, antibacterial, antitumor and anti-inflammatory agents.[2] Moreover, several alkaloids containing the dihydropyrimidine target have been isolated from marine sources, which also exhibited interesting biological properties.[3] For example, batzelladine alkaloids have been utilized as potent HIV gp-120-CD4 inhibitors.[4] Therefore, the synthesis of these heterocyclic compounds has gained special attention. A literature search shows that the preparation of dihydropyrimidinones contains a three component condensation reaction of aldehydes, β-keto esters and urea in acidic solution of EtOH as shown by the pioneer work of Biginelli.[5] The major drawback of this protocol is the low yields in the case of both substituted aromatic and aliphatic aldehydes. Therefore, the search for finding milder and more convenient methods for the preparation of dihydropyrimidinones continued to attract attention. Recently, many improved procedures have been reported for the preparation of DHPMs using $InBr_3$,[6] $InCl_3$,[7] $LiClO_4$,[8] $FeCl_3{\cdot}6H_2O$ or $NiCl_2{\cdot}6H_2O$,[9] *p*-TsOH,[10] $LaCl_3{\cdot}7H_2O$,[11] $Bi(OTf)_3$,[12] $BF_3{\cdot}OEt_2$[13] as catalyst. Polyphosphate ester (PPE)[14] has also been used as a reaction mediator for Biginelli condensation under microwave irradiation. However, many of these protocols suffer from drawbacks such as the use of expensive and highly acidic catalysts and also need prolonged reaction times. Furthermore, the yields of the corresponding DHPMs are not always satisfactory. On the other hand, *N*-bromosuccinimide (NBS) is a very cheap and safe reagent that has extensively been used as oxidizing and brominating agent in organic synthesis.[15] However, the catalytic behavior of NBS as Lewis acid has been firstly studied in our laboratories during a research program in order to find a mild procedure for the acetalization of carbonyl compounds.[16] It was shown that NBS catalyzes selective acetalization of aldehydes in the presence of ketones under mild and neutral reaction conditions. Subsequently, NBS has exponentially been utilized as a mild and almost neutral either a Lewis acid or a reagent for different types of functional group transformations. For example, acetylation of alcohols,[17] preparation of acylals,[18] cleavage of oxathiacetals,[19] interchange of thioacetals and oxathioacetals into their acetals,[19] transesterification, oxathioacetalization, thio-acetalization and *trans*-thioacetalization of carbonyl compounds[20] have also been achieved using NBS under mild reaction conditions. In continuation of this study, herein, we wish to report a facile and improved protocol for preparation of DHPMs under nearly neutral reaction conditions using NBS as catalyst (Scheme 1).

When a mixture of benzaldehyde and ethyl acetoacetate was allowed to react with urea in the presence of NBS (20 mol%) in refluxing EtOH for 10 hours, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-1*H*-one was obtained in 94% yield (Table 1, entry 1). In a similar way, various types of aromatic aldehydes containing either electron-withdrawing or electron-donating substituents as well as cinnamaldehyde successfully react with both urea and thiourea to afford the corresponding 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-1*H*-one and their corresponding sulfur analogs, respectively, in good



Scheme 1

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to excellent yields (Table 1, entries 2–14). Furthermore, under similar reaction conditions, both butanal and heptanal as a model for aliphatic and enolizable aldehydes gave the corresponding 5-ethoxycarbonyl-6-methyl-4-alkyl-3,4-dihydropyrimidine-2-1*H*-one in high yields (entries 15 and 16). Moreover, application of microwave irradiation has opened a new perspective in synthetic organic chemistry, not only in terms of high yield and selectivity, but also ease of the reaction conditions and rate acceleration.[11] Hence, microwaves have been applied to accelerate reaction rates for a variety of chemical transformations and improve the yields of products in most cases. Along this line we observed that, when a mixture of ethyl acetoacetate, benzaldehyde and urea in EtOH (95%) was irradiated with microwave (600 W power) in the presence of a catalytic amount of NBS (20 mol%), the reaction was almost completed within 3 minutes. Work-up of the reaction mixture shows that 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-1*H*-one was prepared in 92% after recrystallization from 95% EtOH (entry 3). The actual role of NBS is not clear so far, as we have mentioned in our previous reports.[16–18] However, a plausible explanation is that NBS might act as a source of Br^+ ions which in turn activates the aldehyde for further reaction with ethyl acetoacetate. Another explanation for this process is that NBS probably generates small quantities of HBr or Br_2, which may be the actual catalyst for the reaction. Since the generation of HBr in protic solvent such as aqueous EtOH is more probable and causes the reaction conditions to became slightly acidic, we have selected *N*,*N*-dimethylacetamide (DMAC). Moreover, owing to the higher solubility of the substrates, and the excellent energy transfer property, it seems that DMAC is a superior solvent than EtOH for this transformation. Under these conditions NBS acts as an almost neutral catalyst through which either Br^+ or Br_2 may be considered as the actual catalyst. Therefore we have chosen DMAC as the reaction solvent in all of the subsequent reactions. In this regard, several types of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-1*H*-ones have been effectively prepared under mild reaction conditions (Table 1). Similarly, 4-alkyl substituted DHPMs were successfully prepared from the reaction of ethyl acetoacetate, urea and aliphatic aldehydes under the same reaction conditions in good yields (entries 15 and 16). Further, the usefulness of this methodology has also been extended to the synthesis of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-1*H*-thiones using thiourea. When NBS (20 mol%) was added to a solution of ethyl acetoacetate, 4-tolylaldehyde and thiourea in DMAC, and the reaction mixture was irra-

Table 1 Synthesis of DHPMs Using NBS as Catalyst Under Microwave Irradiation

Entry	RCHO	X	Time (h)	Yield (%)[a,b]	Time (min)	Yield (%)[a,b]
			Refluxing in EtOH		Irradiated in DMAC	
1	PhCHO	O	10	94	3	92
2	PhCHO	S	15	88	5	80
3	PhCHO	O	3	92[c]	–	–
4	4-MeC_6H_4CHO	O	4	91[d]	–	–
5	4-MeC_6H_4CHO	O	10	90	4	94
6	4-MeC_6H_4CHO	S	16	90	6	89
7	4-$MeOC_6H_4CHO$	O	12	89	4	91
8	4-$MeOC_6H_4CHO$	S	1	90	4	92
9	4-ClC_6H_4CHO	O	15	88	6	89
10	4-ClC_6H_4CHO	S	20	75	6	80
11	4-$NO_2C_6H_4CHO$	O	25	85	6	88
12	4-$NO_2C_6H_4CHO$	S	25	78	6	80
13	Cinnamaldehyde	O	20	90	6	89
14	Cuminaldehyde	O	20	85	5	80
15	$CH_3CH_2CH_2CHO$	O	10	88	4	84
16	$CH_3CH_2CH_2CH_2CH_2CHO$	O	11	85	5	82

[a] Isolated yield.
[b] Products were identified by the comparison of their mp (bp), IR, and ^1H NMR data with those of the authentic samples.
[c] The reactions were carried out under microwave irradiation for 3 min.
[d] 4 min under microwave irradiation.

diated (600 W), the reaction was completed within 3 minutes and 5-ethoxycarbonyl-6-methyl-4-tolyl-3,4-dihydropyrimidine-2-1*H*-thione was obtained in 87% yield. By this procedure different types of structurally diverse 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-1*H*-thiones were prepared from the condensation reactions of various aromatic aldehydes, bearing either electron-withdrawing or electron-releasing substitutents, with thiourea and ethyl acetoacetate under microwave irradiation (entries 2, 6, 8, 10 and 12).

In summary we have introduced a new application for NBS. High yields of the products, short reaction times in the case of microwave irradiation and also mild reaction conditions make this protocol complementary to the existing methods. Further applications of NBS in organic transformation are currently being studied in our laboratories.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 250 or 500 MHz spectrometer in $CDCl_3$ as solvent and with TMS as an internal standard. All of the products are known and gave satisfactory IR and NMR spectra.

Preparation of 5-Ethoxycarbonyl-6-methyl-4-toluyl-3,4-dihydropyrimidine-2-1*H*-one using NBS in Refluxing EtOH (95%); Typical Procedure

A solution of ethyl acetoacetate (1.30 g, 10 mmol), 4-tolylaldehyde (1.2 g, 10 mmol), urea (0.84 g, 14 mmol) and NBS (0.36 g, 2 mmol) in 95% EtOH was heated under reflux for 10 h (Table 1, entry 5). Then the volume of the solvent was reduced to one half and the solution was allowed to cool to r.t. The precipitate was filtered off, washed with H_2O and recrystallized from 95% EtOH to afford pure DHPM as a white solid; yield: 2.5 g (90%); mp 172–174 °C (lit.[13] 172 °C).

Preparation of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-1*H*-one using NBS in EtOH (95%) under Microwave Irradiation; Typical Procedure

A mixture of ethyl acetoacetate (1.30 g, 10 mmol), benzaldehyde (1.1 g, 10 mmol), urea (0.84 g, 14 mmol) and NBS (0.36 g, 2 mmol) in 95% EtOH (3 mL), contained in a tall beaker, was placed in the microwave oven. The beaker was covered with a watch glass and irradiated at 600 W power for 3 min (Table 1, entry 1). To control the evolution of EtOH from the reaction mixture and to prevent splashing, irradiation sequences reaction was interrupted after every 20 s. Then the reaction mixture was allowed to cool to r.t., and 95% EtOH (5 mL) was added. The precipitate was filtered off and washed with H_2O. After drying the almost pure product was obtained as a yellow-white solid; yield: 2.4 g (92%); mp 203–205 °C (lit.[13] 202–204 °C).

Preparation of 5-Ethoxycarbonyl-6-methyl-4-cuminyl-3,4-dihydropyrimidine-2-1*H*-one using NBS in DMAC under Microwave Irradiation; Typical Procedure

A mixture of ethyl acetoacetate (1.30 g, 10 mmol), cuminaldehyde (1.48 g, 10 mmol), urea (0.84 g, 14 mmol) and NBS (0.36 g, 2 mmol) in DMAC (2 mL), contained in a tall beaker, was placed in the microwave oven. The beaker was covered with a watch glass and irradiated at 600 W power for 5 min (Table 1, entry 14). To control the evolution of EtOH from the reaction mixture and to prevent splashing or frothing, irradiation sequences reaction was interrupted after every 20 s. Then the reaction mixture was allowed to cool to r.t., and H_2O (5 mL) was added. The precipitate was filtered off and washed with H_2O. After column chromatography on silica gel (EtOAc–*n*-hexane, 10:1) pure product was obtained as white crystals; yield: 2.4 g (80%), mp: 157–159 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.15 (s, 1 H), 7.67 (s, 1 H), 7.18–7.13 (dd, *J* = 8.15 Hz, 4 H), 5.11 (s, 1 H), 4.00–3.96 (q, *J* = 7 Hz, 2 H), 2.84–2.82 (sep., *J* = 6.8 Hz, 1 H), 2.23 (s, 3 H), 1.17–1.15 (d, *J* = 6.8 Hz, 6 H), 1.11–1.08 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.91, 152.77, 148.66, 147.91, 142.89, 126.77, 126.70, 99.99, 59.70, 54.13, 33.62, 24.42, 24.37, 18.31, 14.61.

Preparation of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-1*H*-thione using NBS in DMAC under Microwave Irradiation; Typical procedure

A mixture of ethyl acetoacetate (1.30 g, 10 mmol), benzaldehyde (1.10 g, 10 mmol), thiourea (1.06 g, 14 mmol) and NBS (0.36 g, 2 mmol) in DMAC (2 mL), contained in a tall beaker, was placed in the microwave oven. The beaker was covered with a watch glass and irradiated at 600 W power for 5 min (Table 1, entry 2). To control the evolution of EtOH from the reaction mixture and to prevent splashing, irradiation sequences reaction was interrupted after every 20 s. Then the reaction mixture was allowed to cool to r.t., and H_2O (5 mL) was added. The precipitate was filtered off and washed with H_2O. After column chromatography on silica gel (EtOAc–*n*-hexane, 10:1) pure product was obtained as yellow-white crystals; yield: 2.15 g (80%); mp 215–217 °C (lit.[7] 220–222 °C).

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