Microwave Synthesis of N-alkyl 3, 4-Dihydropyrimidin-2 (1*H*)-ones and their Thione Analogues in Presence of Phase Transfer Catalyst

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Abstract:
Under microwave synthesis a number of 3, 4-Dihydropyrimidin-2 (1H)-ones reacts remarkably fast with sodium hydroxide, tetrabutyl ammonium bromide (PTC) and alkyl halide using ethanol solvent. Reaction mixture on irradiation in microwave oven at 600 Watt for 115 to 260 seconds gives N-alkyl 3, 4-Dihydropyrimidin-2 (1H)-ones in 81 to 92 % yield.

Key word: Microwave oven, Dihydropyrimidin, alkyl halide, sodium hydroxide, tetrabutyl ammonium bromide.

Introduction:

Describing more than one century ago by Biginelli Dihydropyrimidinones (DHPMS) have now been recognized as vital drugs in the antihypertensive treatment as well as calcium channel blockers, α-1a antagonists and neuropeptide Y (NPY) antagonists.[1] Some of them are batzelladine alkaloids which have been found to be potent HIV gp-120 - CD4 inhibitors.[2] Dihydropymidinone and their sulpher analogues are pharmacologically important because of their antibacterial, antitumor and anti-inflammatory activities[3] The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropymidinone moiety in the corresponding molecule.[4]

In 1893 Biginelli[5] reported the synthesis of DHPMS by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea. In next decades the original cyclocondensation reaction had been extended widely to include variation in all three components, allowing access to a large number of products particularly in the case of substituted aromatic and aliphatic aldehydes. Recently several methods have been reported for preparing Dihydropyrimidine using Lewis acid such as $BF_3.OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$ $ZnCl_2$, $ZnBr_2$, $ZrCl_4$, $BiCl_3$, $Bi(OTf)_3$, LiBr, $LiClO_4$, $Mn(OAc)_3$, CAN, $FeCl_3.6H_2O$, $NiCl_2.6H_2O$ etc.[6] as well aprotic acids such as H2SO4 HOAc, Conc. HCl[7] as promoters. Other methods including ionic liquids and clay[8] are also reported. However, most of these methods are associated with expensive and toxic reagents, stoichiometric amount of catalyst, long reaction time, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Moreover, some of those methods are only practical for aromatic aldehydes.[9-11] Thus there is still a need for a simple and general procedure for one-pot synthesis of

dihydropymidinone and their thione analogues under mild conditions.

Many methods are now a days available for synthesizing libraries of DHPMs of the Biginelli type. These includes standard solution-phase methods, the use of polymer-supported catalysts and the use of polymer supports where one of the three building blocks is anchored to a solid-phase resin, a fluorous-phase tag, or soluble polymer, i.e., a dendrimer.[12] Knowing the diversity in building block selection that is tolerated in the Biginelli reaction, it is evident that a large number of DHPM derivatives of the general formula can be synthesized by combination of a relatively small number of (commercially available or proprietary) individual building blocks. Employing aldehydes, acidic carbonyl derivatives and (thio) urea analogues (points of diversity X and R^3) in a Biginelli-type condensation would lead to a library of 1000 DHPM compounds, with a total diversity points around the DHPM core.[13]

The large number of DHPM derivatives that can be prepared in a one-pot Biginelli multi component reaction, it is clear that a much larger number of very interesting heterocycles having the DHPM scaffold can be obtained by chemical functionalization of the diversity points around the DHPM core. Dihydropyrimidinones possess a rather acidic *N*1-H due to the presence of an enamide moiety (O=C-C=C-NH). Therefore, the *N*1 proton is removed first by treatment with base. Thus, DHPMs are alkylated regiospecifically at N1 when adding alkyl halides in the presence of a suitable base.[14]

The study of *N*-1 substituted DHPMs facilitates supplementing information about structural requirements important to biological activity. It also affords to expand the existing structure–activity relationships and potential to discover additional structure modifications consistent with improved biological activity. The newly synthesized compounds were screened for their calcium channel blocking activity based on their ability to relax a membrane depolarization induced contraction of vascular smooth muscles.[15]

Experimental

All compounds were characterized by modern spectral and elemental techniques. IR spectra was recorded in KBr disc on a Perkin Elmer spectrometer for all products ^{1}H-NMR spectra was recorded on NMR spectrometer in $CDCl_3$ using chloroform as an internal standard. The mass spectra was recorded on GCMS-QP 2010 mass spectrometer. All the reagents used were of AR grade and were used without further purification. The reactions were carried out in microwave oven (CE2977 Samsung).

Synthesis of N-alkyl 3, 4-dihydropyrimidin-2 (1H)-ones and their Thione analogues.

Different 3,4 -dihydropyrimidinones (5.0 mmol), sodium hydroxide (20 mmol), 5 ml of alcohol and tetrabutyl ammonium bromide (0.50 mmol) as a catalyst were taken in 50 ml beaker, stirred for few seconds and placed in microwave oven for irradiation at 600 Watt for 30 second to get 3,4 -dihydropyrimidinone salt. The mixture was cooled at room temperature. The alkyl halide (7.5 mmol) was added to the resulting mixture and was irradiated in microwave oven at 600 Watt for 115 to 260 seconds to get *N* – alkyl 3, 4 -dihydropyrimidinone. The reaction was monitored by TLC. After completion of the alkylation reaction the content was cooled to room temperature. The reaction mixture was poured in ice water (20 ml) and washed with (2 x 25 ml) 2N hydrochloric acid to remove

unreacted salt. The crude product was purified by crystallization using ethanol as a solvent to get pure product.

All the synthesized compounds (1**a-1j) (Table 1)** were characterized by spectral analysis.

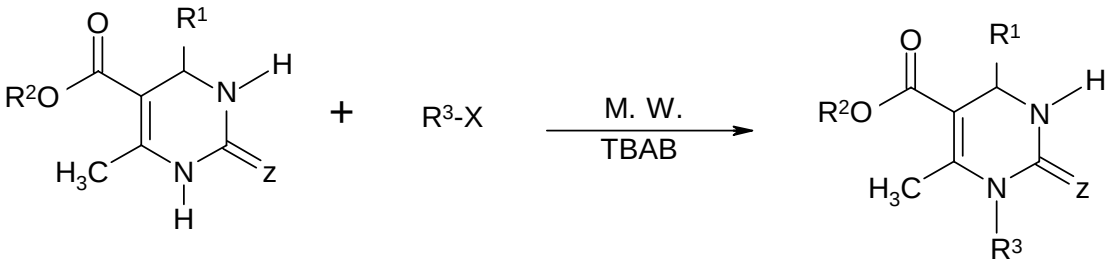
1a. ethyl 3, 6-dimethyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate.

FT-IR (KBr, ν cm^{-1}): 3243 (N-H), 3117 (C-H aromatic), 2957, 2834 (C-H aliphatic), 1702 (C=O), 1461 (-CH_2), 1489 (-CH_3), 1323 (C-O ether).

^{1}H-NMR (DMSO-d6) : δ = 9.34 (s, 1H, NH), 7.91 (s, 1H, NH), 7.55-7.32 (m, 5H Aroma,), 5.28(s, 1H), 4.22-4.02(q, 2H) 3.46 (s, 3H, CH3), 2.41 (s, 3H, CH3), 1.27 (t,3H, CH3) Mass (ES/MS) : m/z 275 (M - H)

Reaction:

N - alkylation of 3, 4 – dihydropyrimidin - 2 (1*H*) - one.



3, 4-dihydropyrimidin-2 (1*H*)-ones

R^1 = methyl aryl, R^2 = methyl, ethyl, R^3 = alkyl, benzyl, and Z = O, S

Results and Discussion

Table - 1 - Physical data of the synthesized compounds (*N* - alkyl 3, 4 -dihydropyrimidin-2 (1*H*)-one) (1a – 1j).

Entry	R^1	R^2	R^3X	Watt W	Time Sec.	Yield (%)	M.P.(°C) Found	M.P.(°C) Reported
1a	C_6H_5	C_2H_5	CH_3I	600	120	89	169	170[27]
1b	C_6H_5	C_2H_5	C_2H_5Br	600	128	86	116	118[27]
1c	C_6H_5	C_2H_5	n-C_3H_7Br	600	115	92	107	108[27]
1d	C_6H_5	C_2H_5	n-C_4H_9Br	600	125	85	108	110[27]
1e	C_6H_5	C_2H_5	n-$C_5H_{11}Br$	600	120	89	120	121[27]
1f	C_6H_5	C_2H_5	CH_2=CH-CH_2	600	260	82	121	122[27]
1g	$C_6H_4(OCH_3)$	C_2H_5	n-C_4H_9Br	600	195	84	120	120[27]
1h	$C_6H_3(OCH_3)_2$	C_2H_5	n-C_4H_9Br	600	190	83	104	105[27]
1i	4 - $NO_2C_6H_4$	CH_3	CH_3I	600	185	81	177	178[35]
1j	CH_3	C_2H_5	n-C_4H_9Br	600	130	82	84	85[27]

The present protocol of *N*-1 alkylation not only preserves the simplicity of synthetic operation. Product yield is moderate to high **(Table- 1)**. The reaction can be performed under relatively simple reaction conditions by stirring together, an appropriate DHPM, sodium hydroxide, tetrabutyl ammonium bromide phase transfer catalyst (PTC) and alkyl halide using ethanol solvent. Reaction mixture on irradiation in microwave oven at 600 Watt for 115 to 260 seconds gives *N*-alkyl DHPMs in 81 to 92% yield.

The present protocol is superior in terms of reaction rate and the yield of products as compared with reports in the literature.

Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of *N* - alkyl 3, 4 - dihydropyrimidin-2 (1*H*)-ones and their thione analogues using tetra butyl ammonium bromide as a eco-friendly, inexpensive and efficient catalyst. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.

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