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Indium catalyzed Microwave-accelerated pot economic C-C bond formation process towards 'dry-media' synthesis of pyrimidine derivatives

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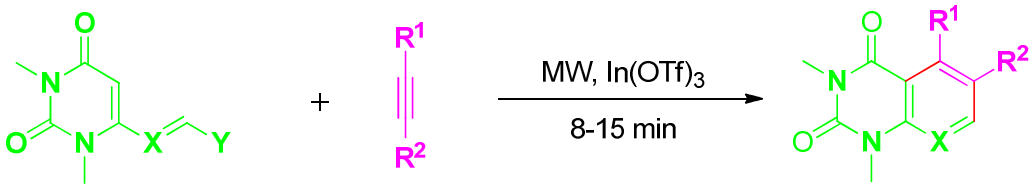
Substituted pyrimidine core containing templates can be constructed within short reaction times in good yields *via* a microwave-accelerated carbon-carbon bond formation process through Lewis acid catalysed Diels-Alder reaction from easily available uracil diene and electron deficient acetylene carboxylate. Emphasis was particularly contributed to explore the diene nature of uracil derivatives with diethylamine moiety in its side chain.



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Indium-catalyzed Microwave-accelerated pot economic C-C bond formation process towards 'dry-media' synthesis of pyrimidine derivatives

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An efficient pot and time economic 'dry-media' synthesis of pyrimidine core containing scaffolds by application of indium triflate catalyzed carbon-carbon bond formation procedure through Diels-Alder reaction using microwaves is described. The method is associated with some attractive characteristics such as short reaction time, high yield of products, and recyclability of recovered catalyst from the reaction mixture.

Introduction

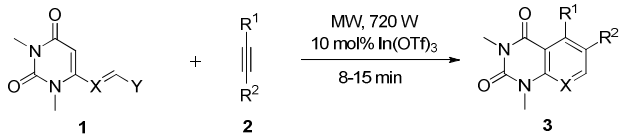
Carbon-carbon bond formation reaction is the center of organic chemistry which offers the foundation for the construction of various functionalized molecules. A rich number of articles were found in literature expressing C-C bond forming reactions for the production of complex molecules from simpler reactants.[1] Application of pot economy[2] principle has chronological significance in heterocyclic chemistry[3] to obtain medicinally interesting molecules.[4] A method is regarded as pot economic if sequential reaction steps are carried out in one reaction vessel without the requirement of work-up and isolation of the intermediate species.The policy of pot economy helps synthetic chemists with an opportunity to form C-C bond efficiently towards the process of synthesizing desired products.

Among numerous methods available in the literature, Diels-Alder process is one of the easiest, yet powerful approaches for C-C bond formation to generate different types of organic molecules. A number of synthetic groups have craftily utilized the Diels-Alder reaction for generation of heterocyclic compounds with stimulating results. For example, Vallejos *et al.* developed both catalyzed and uncatalyzed Diels-Alder reaction strategies between pinacol alkenylboronates and cyclopentadiene to obtain corresponding boronate cycloadducts.[5a] 3,4-Dihydrobenzopyran, an oxo-Diels-Alder product was synthesized by Taylor and Batey by the reaction of in situ-generated cationic aryl 2-oxadiene oxocarbenium ions with alkenes.[5b] Additionally, our group has published an inverse-electron-demand aza-Diels-Alder method for the synthesis of 2,3,4-trisubstituted tetrahydroquinolines from a mixture of aldehydes, anilines, and isoeugenol derivatives.[5c] Development of several families of Diels-Alder reaction thus elevated more attention among synthetic chemists for this area with aim to plan, implement and monitor organic synthesis towards fabrication of important heterocycles.

The spectrum of compounds containing pyrimidine ring system has drawn considerable devotion from chemists as well as biologists because of their pharmaceutical and pharmacological activities. Proven therapeutic efficacies with infinite bioactivities[6] have scatteredaroma to the sphere of pyrimidine containing templates. Some interesting reports from groups of Singh,[7a] Corban,[7b] and Gibson[7c] have shown that pyrimidine derivatives are responsible for biological activities with antimalarial, antithyroid, and antifolate properties, respectively. These applications are accountable for the reputation of pyrimidine chapter that it enjoys in the field of synthetic organic chemistry.

Uracil or pyrimidine-2,4-diones possessing suitable side chain in the ring are very easily susceptible to undergo one-pot, Diels-Alder reaction to produce complex heterocycles in an efficient manner.Very recently, we have shown that pyrido[2,3-*d*]pyrimidine derivatives can be formed from 1,3-dimethyluracil having morpholino methylene amino side chain at the 6-position following a multi-component aza-Diels-Alder reaction strategy.[8a] Our group was also involved with Diels-Alder process towards the syntheses of differently substituted quinazoline dione derivatives.[8b-c] We also found that production of pyrimidine derivatives were possible under microwave irradiations from substituted uracil in 'dry-media' condition.[8d-e]

Designing an efficient, rapid and reliable process to furnish desired products from easily available starting materials avoiding toxic solvents has always been the epicenter during chemical synthesis. Microwave-assisted solid-state reactions has achieved tremendous success in this scenario and are associated with notable advantages such as no use of toxic solvents, easy work-up procedure and short reaction time.[9] With the help of the versatile nature of solid-state microwave synthesis[10] we have synthesized a plethora of compounds during our research studies, focusing on indium(III)-catalyzed processes.[10c-g] As a part of our continued interest in the indium(III)-catalyzed synthesis of nitrogen containing heterocycles, we wish to unveil in this paper a microwave-mediated, solvent-free and Lewis acid-catalyzed new Diels-Alder development to produce pyrimidine core containing heterocycles from uracils and electron-deficient acetylene carboxylates (Scheme 1).



1 2 3

Scheme 1 Microwave-promoted 'dry-media' synthesis of quinazolines and pyrido[2,3-*d*]pyrimidines in one-pot condition.

Results and discussion

Our initial effort to carry out the model reaction of 6-(2-morpholinovinyl)-1,3-dimethyluracil (**1a**, 1.0 mmol) and methyl propiolate (**2a**, 1.2 mmol) with proper reaction condition of solvent, catalyst and temperature, and the results obtained are indicated in Table 1. The reaction was tried to initiate in the absence of catalyst in different solvents under reflux conditions but it did not occur (entries 1-10, Table 1). We then we applied 5 mol% indium triflate to the reaction mixture and interestingly although poor yield, progress of the reaction was observed (*via* TLC) in solvents such as dioxane, toluene, *o*-xylene and DMF, whereas use of water and solvents with relatively lower boiling points gave negative results (entries 11-18, Table 1). Next, we studied the reaction in three solvents (toluene, *o*-xylene and DMF) in presence of 10-15 mol% of the catalyst but unfortunately, we were unable to get any encouraging results. We then changed our strategy and applied microwave energy to carry out the reaction. We found that toluene and *o*-xylene again showed partial conversion into products under microwave condition. Surprisingly, 'dry-media' utilization of 6-(2-morpholinovinyl)-1,3-dimethyluracil (**1a**, 1.0 mmol) and methyl propiolate (**2a**, 1.2 mmol) with 5 mol% $In(OTf)_3$ in a microwave reactor at 720 W afforded methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate (**3a**) with 70% yield within 15 minutes (entry 19, Table 1). In order to obtain more satisfactory yield of the product, we screened a set of solid-state microwave-mediated reactions with 6-(2-morpholinovinyl)-1,3-dimethyluracil (**1a**, 1.0 mmol) and methyl propiolate (**2a**, 1.2 mmol) with different metal triflates/halides and variation in temperature. Our schemes to form desired product by employing indium, copper and, zinc halides showed no significant improvement in reaction yields (entries 27-30, Table 1). In addition, we observed that the temperature deviation during microwave treatment lowered the yield of products (115 ^oC, 50%; 130 ^oC, 65%). Therefore, microwave irradiation of 720 W at 120 ^oC for 15 minutes with 10 mol% $In(OTf)_3$ in 'dry-media' were found to be the 'best media' to obtain the better yield of the desired cyclized products. Having established the optimized reaction conditions for the production of desired heterocycles we then proceeded further to explore the generality of the reaction scheme with different uracils (**1**) and electron deficient acetylene carboxylates (**2**) and results are outlined in Table 2.

The feasibility of our reaction scheme was established by generalization studies which indicated that the reaction condition was well-tolerated by various uracil derivatives[11] and electron deficient acetylene carboxylates. Interestingly, when we applied 6-(morpholinomethyleneamino)-1,3-dimethyluracil in place of 6-(2-morpholinovinyl)-1,3-dimethyluracil and carried out reactions with electron deficient acetylene carboxylates, we observed that the desired products were formed with striking results in comparatively less time (Table 2, entries 13-16 vs 1-4). The success of our methodology with these two sets of reactions inspired us to study further the scope of the reaction with four

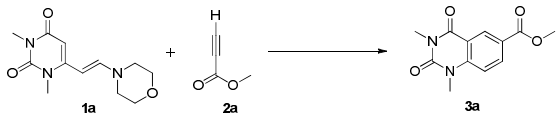


Table 1 Optimization studies for synthesis of **3a**[a]

Entry	Solvent	Catalyst (mol%)	Yield [c](%)
1	Water	-	NR[b]
2	DCM	-	NR[b]
3	DCE	-	NR[b]
4	MeOH	-	NR[b]
5	EtOH	-	NR[b]
6	MeCN	-	NR[b]
7	Dioxane	-	NR[b]
8	Toluene	-	NR[b]
9	*o*-Xylene	-	NR[b]
10	DMF	-	NR[b]
11	Water	$In(OTf)_3$ (5)	NR[c]
12	DCE	$In(OTf)_3$ (5)	NR[c]
13	EtOH	$In(OTf)_3$ (5)	NR[c]
14	MeCN	$In(OTf)_3$ (5)	NR[c]
15	Dioxane	$In(OTf)_3$ (5)	Trace[c]
16	Toluene	$In(OTf)_3$ (5)	Trace[c]
17	*o*-Xylene	$In(OTf)_3$ (5)	Trace[c]
18	DMF	$In(OTf)_3$ (5)	Trace[c]
19	Neat	$In(OTf)_3$ (5)	70[d]
20	Neat	$In(OTf)_3$ (10)	89[d]
21	Neat	AgOTf (10)	85[d]
22	Neat	$Cu(OTf)_2$ (10)	85[d]
23	Neat	$Sc(OTf)_3$ (10)	84[d]
24	Neat	$Yb(OTf)_3$ (10)	80[d]
25	Neat	$Zn(OTf)_2$ (10)	85[d]
26	Neat	$In(OTf)_3$ (15)	85[d]
27	Neat	$InCl_3$ (10)	40[d]
28	Neat	$InBr_3$ (10)	40[d]
29	Neat	$CuCl_2$ (10)	Trace[d]
30	Neat	$ZnCl_2$ (10)	Trace[d]

[a] Reaction conditions: a mixture of 6-(2-morpholinovinyl)-1,3-dimethyluracil (**1a**, 1.0 mmol) and methyl propiolate (**2a**, 1.2 mmol) was refluxed in different solvents [b] without catalyst; [c] with indium triflate for 6 h; [d] was irradiated with catalysts at 720 W inside a microwave reactor in 'dry-media' for 15 min. [e] Isolated yield.

different uracil analogs. We found repetitions of above experiments with these modified uracil molecules furnished products with comparable yields. It is noteworthy that all uracil derivatives synthesized from N,N-dimethyl-6-aminouracil could construct products with more yields within a shorter time (8-10 min) than their analogous counterparts prepared from N,N-dimethyl-6-methyluracil (12-15 min, Table 2). These results not only support the versatility of well-documented microwave-mediated $In(OTf)_3$ catalyzed procedures but also strengthen the already recognized reports about the regioselective nature associated with these kind of [4+2]-cycloaddition reactions with appropriately substituted uracils.[8b] However, our effort to fabricate reactions between uracil analogs and phenyl acetylenes failed, as no indication about the formation of products was observed after a reaction time of 20 min. It can be mentioned here that in all cases a little amount of reactants remained after usual work-up which could be removed during column chromatography. We also tried for an alternative technique for separation of products. Gratifyingly, we found that the pyrido[2,3-*d*]pyrimidines could be separated from the reaction mixture after cooling it to room temperature followed by crystallization from methanol-dichloromethane mixture. But, this process was impracticable to produce pure quinazoline derivatives and so column chromatography technique was carried out to get the pure products from 6-(2-morpholinovinyl)-1,3-dimethyluracil, 6-[2-(diethylamino)vinyl]-1,3-dimethyluracil and, 6-[2-(dimethylamino)vinyl]-1,3-dimethyluracil. All the products obtained were characterized by spectroscopic analyses.

Table 2 Direct synthesis of quinazolines and pyrido[2,3-*d*]pyrimidines[a]

Entry	X	Y	R^1	R^2	Product	Time (min)	Yield[b] (%)
1	CH	$N(CH_2CH_2)_2O$	H	COOMe	**3a**	15	89, 81*, 65**
2	CH	$N(CH_2CH_2)_2O$	H	COOEt	**3b**	15	89
3	CH	$N(CH_2CH_2)_2O$	COOMe	COOMe	**3c**	12	88
4	CH	$N(CH_2CH_2)_2O$	COOEt	COOEt	**3d**	12	87
5	CH	$N(CH_2CH_3)_2$	H	COOMe	**3a**	15	86
6	CH	$N(CH_2CH_3)_2$	H	COOEt	**3b**	15	85
7	CH	$N(CH_2CH_3)_2$	COOMe	COOMe	**3c**	12	84
8	CH	$N(CH_2CH_3)_2$	COOEt	COOEt	**3d**	12	82
9	CH	$N(CH_3)_2$	H	COOMe	**3a**	15	83
10	CH	$N(CH_3)_2$	H	COOEt	**3b**	15	83
11	CH	$N(CH_3)_2$	COOMe	COOMe	**3c**	12	83
12	CH	$N(CH_3)_2$	COOEt	COOEt	**3d**	12	82
13	N	$N(CH_2CH_2)_2O$	H	COOMe	**3e**	10	92
14	N	$N(CH_2CH_2)_2O$	H	COOEt	**3f**	10	92
15	N	$N(CH_2CH_2)_2O$	COOMe	COOMe	**3g**	8	91
16	N	$N(CH_2CH_2)_2O$	COOEt	COOEt	**3h**	8	90
17	N	$N(CH_2CH_3)_2$	H	COOMe	**3e**	10	90
18	N	$N(CH_2CH_3)_2$	H	COOEt	**3f**	10	89
19	N	$N(CH_2CH_3)_2$	COOMe	COOMe	**3g**	8	89
20	N	$N(CH_2CH_3)_2$	COOEt	COOEt	**3h**	8	89
21	N	$N(CH_3)_2$	H	COOMe	**3e**	10	91
22	N	$N(CH_3)_2$	H	COOEt	**3f**	10	91
23	N	$N(CH_3)_2$	COOMe	COOMe	**3g**	8	90
24	N	$N(CH_3)_2$	COOEt	COOEt	**3h**	8	90

[a] Reaction conditions: uracils (**1**, 1.0 mmol), electron deficient acetylene carboxylates (**2**, 1.2 mmol) and $In(OTf)_3$ (10 mol%) were irradiated with 720 W in a microwave reactor without solvent for appropriate time. [b] Isolated yield. Catalyst recyclability[12] after *third cycle and **fourth cycle.

Although a detailed mechanistic study was not carried out we envisaged that $In(OTf)_3$ coordinated with methyl/ethyl propiolate by replacing hydrogen atom and thus activating it as an efficient dienophile for a facile and faster [4+2]-cycloaddition reaction with uracil molecule. We performed a reaction between 6-(2-morpholinovinyl)-1,3-dimethyluracil and methyl propiolate under microwave conditions of 720 W in absence of $In(OTf)_3$ and observed no transformation despite longer reaction time (20 min) which supported the role of $In(OTf)_3$ in the reaction.

Inspired by these results we extended our study to examine the scope of the reaction scheme in conventional heating process. We have tried to shed some light on two molecules; 6-[2-(diethylamino)vinyl]-1,3-dimethyluracil and 6-[(diethylamino) methylene]amino-1,3-dimethyluracil, as there is no report available in the literature about the formation of cycloadducts from these two molecules. Accordingly, uracil with diethylamine moiety in the side chain (**4**, 1.0 mmol), acetylene carboxylate (**2**, 1.2 mmol) and $In(OTf)_3$ (10 mol%) was finely ground in an alumina mortar and the well-homogenized mixture was heated without solvent in an oil bath at 120 ^oC. It was found that the desired cyclized products were formed after 10 h with 60-70% yields (Fig. 1). This observations made it clear that the reaction was accelerated by $In(OTf)_3$ under microwave condition and it was further confirmed that products could be obtained from 6-[(diethylamino)methylene]amino-1,3-dimethyluracil in higher amounts in comparison to 6-[2-(diethylamino)vinyl]-1,3-dimethyluracil. Further increase in reaction time did not report any progressive result in yields. To the best of our knowledge, this is the first report on the synthesis of pyrimidine core containing heterocyclic compounds using uracil derivatives with diethylamine moiety in its side chain in 'dry-media' condition. Efforts are required to explore the synthetic potential of this special class of uracils to form novel and complex molecules.

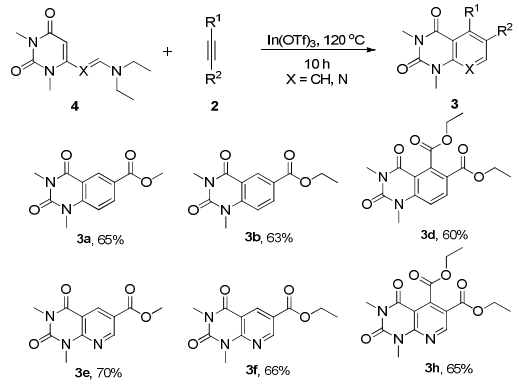


Fig. 1'Dry-media' synthesis of quinazolines and pyrido[2,3-*d*]pyrimidinesunder thermal conditions.

Conclusions

In summary, a direct and economical indium triflate catalyzed Diels-Alder method is successfully demonstrated for synthesizing pyrimidine core containing annelated heterocycles with high yields in a microwave-accelerated solvent-free condition. Extensive investigations are also carried out on the effect of leaving groups of uracil system on the yield of products under this one-pot procedure. This can relieve the serious problems of longer reaction time, use of toxic solvents during synthesis, tedious work-up procedure, and demand of multiple reaction vessels. Furthermore, the combination of advantages of this methodology such as catalyst recovery and recyclability together with generation of products with minimal waste production make our effort interesting towards formation of desired compounds.

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Notes and references

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