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# The Synergy of Combined Use of DMSO and Bronsted Acid (Ionic Liquid) as a Catalyst

## ——Part I: Efficient Niementowski synthesis of modified quinazolinones

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## Abstract

A new rapid and versatile approach using Ionic Liquid/DMSO as a chemical reagent for the synthesis of fused heterocyclic compounds in a highly efficient way is described. This method offers the advantages of proceeding in neutral conditions, giving high to excellent isolated yields (83-92%) for Niementowski synthesis with easy workup procedure. The inherent Bronsted acidity of ionic liquid and high polarity of both IL and DMSO resulted in a significant enhancement in the reaction rate.

**Keywords:** Ionic Liquids, DMSO, Niementowski

## 1. Introduction

Rutaecarpine type alkaloids constitute an important class of indolopyridoquinazolinone heterocycles, which belong to the subgroup of quinazoline type alkaloid, belonging to *Rutaceae* family [1]. Rutaecarpine (**Figure 1**) shows a variety of pharmacological activities including antithrombotic [2], vasorelaxant [3], cyclooxygenase (CoX-2) inhibitor [4,5], thermoregulatory, anti-obesity [6], as well as effects on the cardiovascular and endocrine systems [7]. The progress in the studies of rutaecarpine has been reviewed [8]. Recently numerous thiophene analogues of rutaecarpine [9] as well as quinazoline have shown good anticancer activity [10], analgesic [11], anti-inflammatory [12-14] as well as antiparkinsonims activity [15]. Bioisosterism is a strategy of medicinal chemistry for the rational design of new drug, applied with a lead compound as a special process of molecular modification [16]. Purine bases and their bioisoteric analogs were widely used as building block in combinatorial chemistry. The bioisoteres of purine bases such as thienopyrimidine and pyridopyrimidine possess wide range of biological activity such as PDE inhibitory activity, antiparkinsonism, CNS depressant, analgesic, anti-inflammatory [17-19] etc.

Since Niementowski's preparation of 4(3*H*)-quinazolinone by fusing anthranilic acid with formamide [20], several methods aimed toward the synthesis of modified quinazolinones have been pursued [21,22]. Recently a series of 1,3,10,12-tetrasubstituted-8*H*-pyrido-[2',3':4,5]-pyrimido[6,1-*b*]quinazolin-8-ones [23] and tetracyclic 1,2,9,11-tetrasubstituted-7*H*-thieno-[2',3':4,5]pyrimido-[6,1-*b*]-quinazolin-7-ones [24] has been reported by Laddha *et al*. However the reaction did not go to completion in our hands as reported by the authors. Each of these methods has one or more of the following drawbacks. For instance, the use of expensive and toxic reagents, harsh reaction conditions, refluxing for a prolonged period of time, tedious work-ups etc. In addition, the known methods made use of volatile organic solvents, leading to complex isolation and recovery procedures. Therefore, we sought to develop a more efficient and convenient method that avoids these drawbacks and could be used on both laboratory as well as industrial scale.

Ionic Liquid (ILs) have been widely recognized as an efficient synthetic tool and its benefit has been well documented. Ionic liquids have been touted as replacements for traditional molecular solvents in synthesis because of most of them are nonvolatility, nonflammability, their stability and ease of recyclability [25]. An extensive

literature describing the diversity of ionic liquids are available [26]. Recently ionic liquid has been designed specifically for nucleophilic aromatic substitutions [27].

Very recently we have investigated the synergy of the combined use of ionic liquid and DMSO in the proportion 0.1:1 to synthesize a variety of esters in remarkably short reaction times from acyl or alkyl halides by their reaction with sodium carboxylates in the above -mentioned mixed solvent medium in the absence of any added catalyst under ambient conditions [28,29].

Till now there is no reported method for Niementowski's synthesis using ionic liquids to the best of our knowledge. We aimed to modify the procedure reported till now using ionic liquids which can be applicable not only for fused quinazoline but to a wide range of fused heterocycles such as substituted thienopyrimidine, pyridothienopyrimidines, triazinoquinazolines as well as quinazolines.

In continuation of our ongoing work on condensed thienopyrimidines and quinazolines [30,31], we herein report the fused heterocyclic derivatives of thienopyrimidine and quinazoline as divalent and ring equivalent isosteres of Rutaecarpine. Hence a series of novel heterocyclic compounds belonging to thienopyrimidine fused with quinazoline, substituted thiophene, pyridothiophene and quinazoline fused with substituted thiophene, pyridothiophene, quinazoline were synthesized using ionic liquid and DMSO. We initiated this study with the goal of expanding the efficacy and efficiency of the methodologies developed by us using ionic liquids for the synthesis of fused heterocycles [32].

## 2. Result and Discussion

The starting material employed thiophene *o*-aminoesters, their subsequent cyclization with formamide and chlorination were done as per our earlier reported method [32]. The latter reaction is either carried out in microwave or by classical heating using polyphosphoric acid. The next step involves the reaction of anthranilic acid and condensed 4-chloro-pyrimidine to give the desired products. It is assumed that formation of products requires an acyl substitution between the pyrimidine nitrogen and the carboxylic acid group.

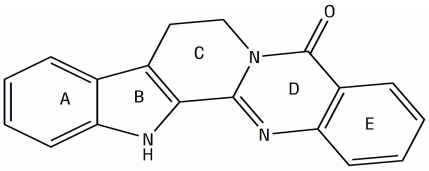


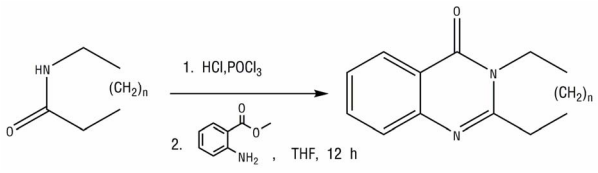

**Figure 1. Structure of rutaecarpine.**

All the present synthetic methodology for condensation reaction have one or the other draw back of lengthy reaction time, high temperature and in many synthesis the use of Volatile Organic Compounds (VOC's) such as tetrahydrofuran (**Scheme 1**) which are detrimental to the environment and solvents that need to be recovered and recycled completely adding to the economics of the process.

Our research work devoted to the combined use of ionic liquid and DMSO in 0.1:1 proportion, we extended the investigation of this system towards the present synthesis. We have exploited this type of reaction by employing cyclic iminochlorides in the synthesis of fused heterocyclic in an attempt to increase the rate of reaction using ionic liquid.

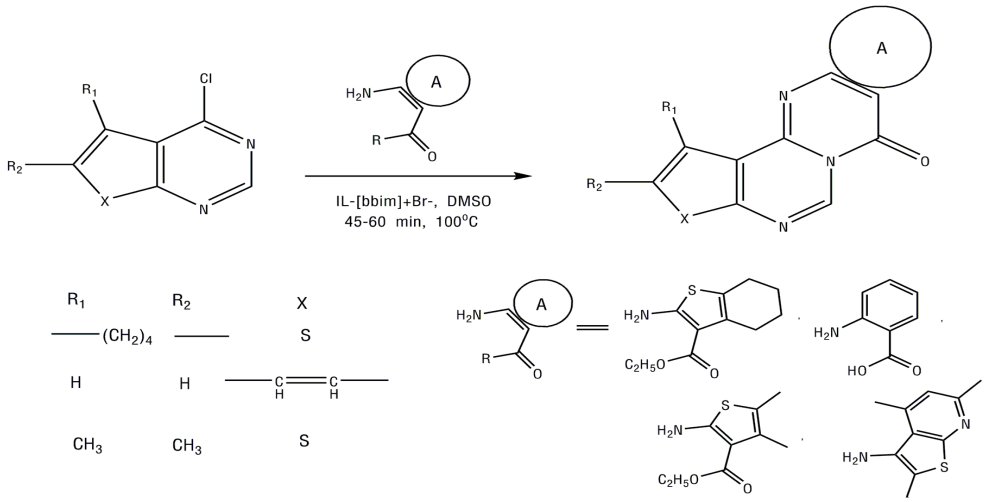
The reaction was initially carried out in DMSO and Ionic liquids $[bbim]^+ Br^-$ independently. However, in DMSO there was no reaction but in ionic liquid the reaction went to completion in 10 hrs. Using the above solvent mixture conditions DMSO/IL (1:0.1 proportion), the reaction was completed in just 45-60 min (**Scheme 2)**. The bronsted acidic IL was responsible for promotion of the reaction. We have successfully done first cyclization step using DMSO/IL in 45-60 minutes (**Table 1**) with better yields and purity. However the conventional heating method of cyclization required 8-24 hr for each reaction. It was observed that under similar conditions, the substrate containing *o*-amino acids underwent condensation with cyclic iminochlorides at a faster rate when compared to *o*-amino esters. Solvents with hydrogen-bond accepting properties can interact with the protons of the acid, increasing the electron density on the nitrogen atom and therefore its nucleophilic character. This increase has been shown when DMSO is used as the solvent. Ionic liquids as bronsted acid can bond with sulphonyl oxygen of DMSO and give rise to dimsyl ion. Dimsyl ion can then interact with amine hydrogen of anthranilic acid as well as thiophenes resulting in naked -NH ions. The naked ion is highly reactive giving rise to the observed reaction.

Thus the use of ionic liquid in synergy with DMSO was found to accelerate and significantly improved the yield and reduced the time of the reaction. The synergy of combined use of IL and DMSO is evident from the observation that the reaction did not proceed at all either in DMSO or in $[bbim]^+Br^-$ individually under similar




**Scheme 1**




**Scheme 2**

conditions. This method offers a route to free carboxylic acid as well as ester condensation. Compared to the reported methods, our method is convenient, safe, and can be performed under ambient conditions with easy isolation procedures by drowning the reaction mixture into ice water. The IL could be recovered from the aqueous filtrate by distillation under reduced pressure. Our particular important achievement is with respect to reaction in the last step which took much shorter reaction time than hitherto reported. The process is amenable to scale up and can be gainfully employed to synthesize a library of condensed thienopyrimidines as well as quinazoline analogues. The overall yield is better than those reported so far.

## 3. Conclusion

We have described a new, rapid and a versatile approach using DMSO and ionic liquid as a chemical catalysts for the synthesis of fused heterocyclic compounds in a highly efficient way. Additional work is in progress to obtain different types of fused heterocycles with various biological activities.

## 4. Experimental

The IL $[bbim]^+Br^-$ is synthesized as per the procedure reported by us [29]. Typical procedure for the reaction of cyclic iminochlorides with *o*-amino acids/esters by the combination of ionic liquid and DMSO. **3*a-j***

A mixture of 4-chlorothieno[2,3-d]pyrimidine (0.044 mol), amino acid/ester (0.045 mol) in $[bbim]^+Br^-$ and DMSO in 0.1:1 (0.5 g:5 g) proportions was heated at 100°C on oil bath for 45-60 minutes. The progress of the reaction was monitored by TLC. The reaction mixture was quenched in ice cold water (30 ml), precipitated solid was filtered, washed with cold water and air-dried. The mixture of IL and DMSO was recovered from the aqueous filtrate by subjecting it to distillation under reduced pressure. The product was pure enough (single spot on TLC) for all practical purposes. However, for characterization purposes it was further purified by column chromatography (30% ethylacetate: *n*-hexane).

1,2,3,4-*Tetrahydro*[9*H*-1]*benzothieno*[2',3':4,5]*pyrimido*6,1-*b*]*quinazolin*-9-*one*

**3*a*:** δH (400 MHz, $CDCl_3$), 1.83 (4H, m, $CH_2$), 2.63 (2H, t, $CH_2$), 2.82 (2H, t, $CH_2$), 7.39 (4H, m, CH), 7.99 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1692 (C=O), 1591 (C=C), 1546 (C=N), 3057 (C-H aromatic stretch); *m/z* 307.2 ($M^+$); Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.46; N, 13.45; Found: C, 66.3; H, 4.2; N, 13.7.

**3*b*:** δH (400 MHz, $CDCl_3$), 1.61 (8H, m, $CH_2$), 1.87 (4H, t, $CH_2$), 2.89 (2H, t, $CH_2$), 2.03 (2H, t, $CH_2$), 7.93 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1562 (C=N), 1680 (C=O), 1588 (C=C), 3040 (C-H aromatic stretch); *m/z* 367.4 ($M^+$); Anal. Calcd. for $C_{19}H_{17}N_3OS_2$: C, 62.10; H, 4.66; N, 11.43; Found: C, 62.0; H, 4.7; N, 11.4.

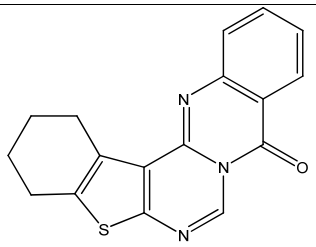
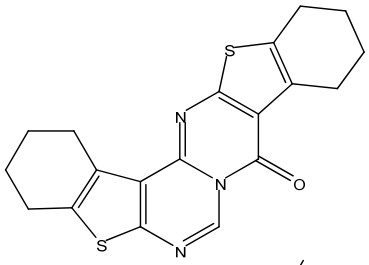
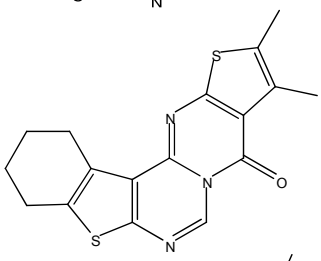
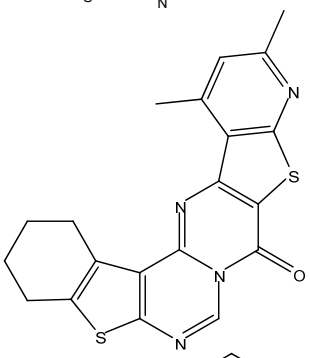
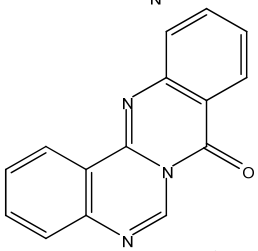
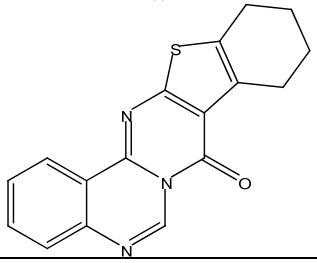
2,3-*Dimethyl*-8,9,10,11-*tetrahydro*-2*H*,3*H*-1,7-*dithia*-4*a*,6,12-*triaza*-*indeno*(5,6-*c*)*fluren*-4-*one*

**3*c*:** δH (400 MHz, $CDCl_3$), 1.84 (4H, m, $CH_2$), 2.39 (3H, s, $CH_3$), 2.47 (3H, s, $CH_3$), 2.78 (2H, t, $CH_2$), 2.96 (2H, t, $CH_2$), 7.80 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1684 (C=O), 1591 (C=C), 1548 (C=N), 3042 (C-H aromatic stretch), 2933 (C-H aliphatic stretch); *m/z* 343.2 ($M^+$); Anal. Calcd. for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23.

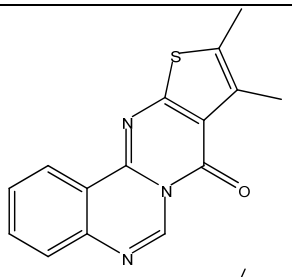
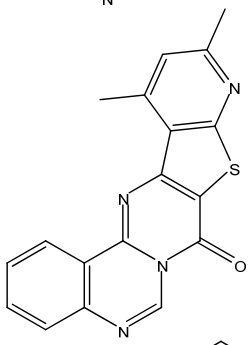
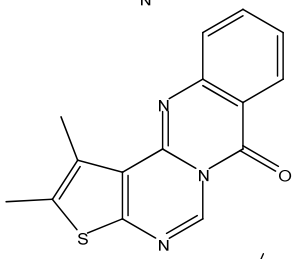
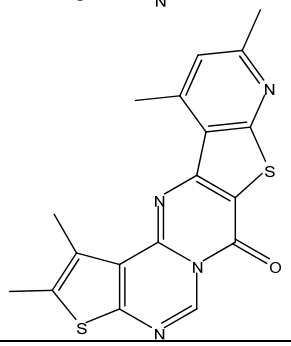
***3d*:** δH (400 MHz, $CDCl_3$), 1.88 (4H, m, $CH_2$), 2.57 (3H, s, $CH_3$); 2.71 (3H, s, $CH_3$), 2.63 (2H, t, $CH_2$), 2.82 (2H, t, $CH_2$), 6.92 (1H, s, CH), 7.95 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1682 (C=O), 1592 (C=C), 1553 (C=N), 3038 (C-H aromatic stretch), 2936 (C-H aliphatic stretch); *m/z* 394.2 ($M^+$); Anal. Calcd. for $C_{20}H_{18}N_4OS_2$: C, 60.89; H, 4.60; N, 14.20; Found: C, 60.5; H, 5.1; N, 14.6.

**Table 1. Ionic liquid and DMSO promoted synthesis of some novel fused heterocycles (3*a*-3*j*).**

| Sr. No | Structure | Ionic liquids | | |
|---|---|---|---|---|
| | | Yield[a] (%) | Mp (°C) | Time (min) |
| **3*a*** |  | 92 | 212-214 | 45 |
| **3*b*** |  | 85 | 233-235 | 60 |
| **3*c*** |  | 83 | 222-224 | 60 |
| **3*d*** |  | 89 | 282-283 | 60 |
| **3*e*** |  | 91 | 205-208 | 45 |
| **3*f*** |  | 85 | 266-268 | 60 |

| | | | | |
|---|---|---|---|---|
| **3*g*** |  | 88 | 245-248 | 60 |
| **3*h*** |  | 90 | 269-273 | 60 |
| **3*i*** |  | 89 | 285-288 | 45 |
| **3*j*** |  | 93 | 297-299 | 60 |

*Quinazollinone*(4,3-*b*)*quinazolin*-8-*one*

**3*e*:** δH (400 MHz, $CDCl_3$), 7.07-7.87 (8H, m, CH), 7.89 (1H, s, CH). $\nu_{max}$ (neat)/$cm^{-1}$: 1682 (C=O), 1608 (C=C), 3026 (C-H aromatic stretch), 1562 (C=N). *m/z* 247.1 ($M^+$). Anal. Calcd. for $C_{15}H_9N_3O$: C, 72.87; H, 3.67. Found: C, 72.9; H, 3.4; N, 17.2.

**3*f*:** δH (400 MHz, $CDCl_3$), 1.81 (4H, m, $CH_2$), 2.68 (2H, t, $CH_2$), 2.86 (2H, t, $CH_2$), 7.33 (4H, m, CH), 7.98 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1706 (C=O), 1605 (C=C), 3007 (C-H aromatic stretch), 1530 (C=N); *m/z* 307.2 ($M^+$); Anal. Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.6; H, 4.5; N, 13.2.

8,9-*Dimethyl*-10-*thia*-5,6*a*,11-*triaza*-*cyclopenta*(*b*)*phenanthren*-7-*one*

**3*g*:** δH (400 MHz, $CDCl_3$), 2.40 (3H, s, $CH_3$), 2.48 (3H, s, $CH_3$), 7.33 (4H, m, CH), 7.95 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1684 (C=O), 1598 (C=C), 1548 (C=N), 3019 (C-H aromatic stretch), 2940 (C-H aliphatic stretch); *m/z* 281.2 ($M^+$). Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 65.2; H, 3.8; N, 15.1.

10,12-*Dimethy*-8-*thia*-5,6*a*,9,13-*tetraaza*-*indeno*(2,1-*b*)-*phenanthren*-7-*one*

**3*h*:** δH (400 MHz, $CDCl_3$), 1H NMR (400 MHz, $CDCl_3$): δ, 2.61 (3H, s, $CH_3$); 2.74 (3H, s, $CH_3$), 6.68 (1H, s, CH), 7.28 (4H, m, CH), 7.86 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1674 (C=O), 1592 (C=C), 1542 (C=N), 2938 (C-H aliphatic stretch); *m/z* 307.2 ($M^+$); Anal. Calcd. for $C_{18}H_{12}N_4OS$: C, 65.04; H, 3.64; N, 16.86, Found: C, 64.8; H, 3.8; N, 16.3.

1,2-*Dimethyl*-7*H*-*thieno*[2',3':4,5]*pyrimido*[6,1-*b*]*quinazolin*-7-*one*

**3*i*:** δH (400 MHz, $CDCl_3$), 2.44 (3H, s, $CH_3$), 2.51

(3H, s, $CH_3$), 7.26 (4H, m, CH), 7.88 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1695 (C=O), 1601 (C=C), 1542 (C=N), 3034 (C-H aromatic stretch), 2938 (C-H aliphatic stretch); *m/z* 281.2 ($M^+$); Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.1; H, 4.2; N, 14.7.

**3*j*:** δH (400 MHz, $CDCl_3$) δ, 2.41 (3H, s, $CH_3$), 2.48 (3H, s, $CH_3$), 2.65 (3H, s, $CH_3$); 2.72 (3H, s, $CH_3$), 6.42 (1H, s, CH), 7.94 (1H, s, CH); $\nu_{max}$ (neat)/$cm^{-1}$: 1690 (C=O), 1610 (C=C), 1554 (C=N), 3018 (C-H aromatic stretch), 2938 (C-H aliphatic stretch); *m/z* 366.4 ($M^+$). Anal. Calcd. for $C_{18}H_{14}N_4OS_2$: C, 58.99; H, 3.85; N, 15.29. Found: C, 59.3; H, 3.6; N, 15.4.

## 5. Acknowledgments

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