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SEQUENTIAL CHANGE IN ONE POT THREE COMPONENT PROTOCOL – A STEPPING STONE IN HETEROCYCLIC SYNTHESIS

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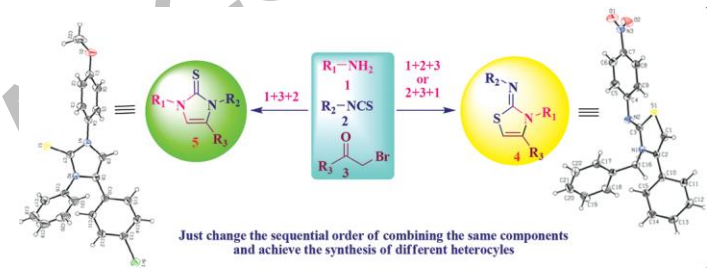
Abstract

As a novel synthetic diversity, two different heterocycles *viz*. thiazole-2-imines and imidazole-2-thiones have been conveniently synthesized by just altering the sequential order (**1+2+3** or **1+3+2**) of combining the same components *viz*. aryl amine (**1**), aryl isothiocyanate (**2**) and phenacyl bromide (**3**) in one pot three component protocols. The third possible sequential order of combination (**2+3+1**) chemoselectively affords thiazole-2-imine. The finding is a stepping stone in the synthetic applicability of sequential one-pot three component protocols.



KEYWORDS: stepping stone, sequential change, thiazole-2-imine, imidazole-2-thione, one-pot, three components

INTRODUCTION

Imidazole-2-thione and thiazole-2-imine derivatives possess a variety of bioactivity.[1–3] There are many protocols for the synthesis of thiazole-2-imine derivatives[4–16] and imidazole-2-thione derivatives[17–25] from different starting materials. However, to the best of our knowledge, there is only a single report,[26] wherein two different five membered heterocycles have been prepared by using the same components. Herein, we report a novel observation, that is, the synthesis of two different heterocycles from the same components by taking into account the various possible inter-component reactivities and subsequently changing the sequence of their combination in a one pot three component reaction.

Three component reactions have emerged as a potential tool in organic syntheses. Some named reactions such as Biginelli condensation, Mannich, Hantzsch, Petasis, Passerini and Strecker reactions have paved the way for the synthesis of diversified heterocyclic compounds. These one pot reactions generally involve the combination of the components giving little importance to the various possible inter-reactivity of the individual components with each of the other components combined. Hence, little emphasis is being given to the sequence of combining the components in many multi-component reactions. One such three component reactions involving aryl amine, aryl isothiocyanate and phenacyl bromide as the components has been reported to afford

thiazole-2-imine.[4–16] On the other hand, in contrast to this Zeng.et.al. have reported that the same three component reaction yield imidazole-2-thione and not the thiazole-2-imine as reported.[24] In continuation of this controversy, Singh. et. al. have revisited to the same three component reaction once again re-establishing their original claim that is the product formed is thiazole-2-imine and not imidazole-2-thione.[27] Though all these reports have resulted in the synthesis of thiazole-2-imine alone *via*. the three component protocol, we herein report that by considering the inter-component reactivities and changing their sequence of combination, it is possible to synthesize both the above said heterocycles *viz*. thiozole-2-imine and imidazole-2-thione.

RESULTS AND DISCUSSION

From a deeper look on these components, it could be envisaged that aryl amine will react with both aryl isothiocyanate and phenacyl bromide separately to afford thiourea and mono phenacyl amine respectively which can further react with the third component to afford two different heterocycles *viz*. thiazole-2-imine (**4**) and imidazole-2-thione (**5**) derivatives respectively (Scheme 1).

In view of the above presumption, the three components were combined by two different sequential orders as shown in Scheme 1 affording **4** and **5** in excellent yields, the details of which are presented vide infra.

At the outset, the first sequential order (**1+2+3**) of combining the components was attempted i.e. aryl amine (**1**) was added to aryl isothiocyanate (**2**) in ethanol to afford

thiourea immediately (as monitored by TLC) to which was added the third component *viz*. phenacyl bromide (**3**) and the mixture was refluxed for about 30 minutes to afford the corresponding thiazole-2-imines in good to excellent yields (Table 1).

On the other hand, the second sequential order of combination (**1+3+2**) of the above said components was attempted *i.e*. aryl amine (**1**) was added to ethanolic solution of phenacyl bromide (**3**) and refluxed for 30 minutes and then aryl isothiocyanate (**2**) was added and further refluxed for 20 minutes. To our delight, this change in the sequential order resulted in the formation of the corresponding imidazole-2-thione (**5**) in good to excellent yield (Table 2).

As a representative example, the intermediate viz. 1,3-diphenylthiourea formed by reaction of aniline (1a) and phenyl isothiocyanate (2a) has been isolated. Similarly, the intermediate viz. mono phenacyl aniline by the reaction of aniline (1a) and phenacyl bromide (3a) has been isolated. These intermediates on reaction with the third component afford the expected products *viz*. thiazole-2-imine (**4a**) and imidazole-2-thione (**5a**) respectively. The intermediates were characterized by comparison of their physical and spectral data with that of the authentic samples.

Finally, the third possible sequential order of combining the three components (**2+3+1**) was also attempted i.e. aryl isothiocyanate (**2**) was added to a solution of phenacyl bromide (**3**) in ethanol followed by the addition of aryl amine (**1**) and the mixture was refluxed. This resulted in the formation thiazole-2-imine (**4**) as the exclusive product

indicating that aryl amine (**1**) chemoselectively reacts with aryl isothiocyanate (**2**) to afford the thiourea which subsequently reacts with phenacyl bromide (**3**) to give the product.

Of the compounds synthesized, except two heterocycles (**4a** and **4b)**[16], others are hitherto unknown. All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR (1D & 2D). X-ray crystal structure of a representative compounds (**4k** and **5k**) unambiguously confirms the structural assignment.

CONCLUSION

The novelty of synthesizing two different heterocycles viz.thiazole-2-imines and imidazole-2-thiones from the same components viz. aryl amine, aryl isothiocyanate and phenacyl bromide through one-pot protocol by just changing the sequential order of combining the components is reported. This interesting observation is a stepping stone in the synthetic applicability of one pot sequential three component protocols in heterocyclic synthesis. It conveys that looking at the various possible inter-component reactivities before planning a multicomponent reaction may pave the way for newer synthetic applicability.

EXPERIMENTAL SECTION

General Procedure For The Synthesis Of Thioazole-2-Imine Derivatives (4)

To the amine (**1**, 1 mmol) in ethanol (3mL), aryl isothiocyanate (**2,** 1 mmol) was added followed by phenacyl bromide (**3,** 1 mmol) and the solution was refluxed for 30 minutes.

After the completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and poured onto excess of crushed ice to afford the corresponding thioazole-2-imine (**4**) as a solid which was filtered and recrystallized from distilled ethanol.

(Z)-N-(3,4-Diphenylthiazol-2(3H)-Ylidene)Aniline **(4a)**[16]

Obtained as a white solid; Mp.191-193 ºC. ^{1}H NMR (300 MHz, $CDCl_3$: δ 7.33 – 7.17 (m, 10H), 7.09 – 6.98 (m, 5H), 5.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.96, 151.84, 139.93, 138.06, 131.69, 129.33, 128.85, 128.77, 128.23, 128.18, 127.44, 123.14, 121.56, 97.21.

General Procedure For The Synthesis Of Imidazole -2-Thione Derivatives **(5)**

To the amine (**1**, 1 mmol) in ethanol (3mL), phenacyl bromide (**3,** 1 mmol) was added and refluxed for 30 minutes and then aryl isothiocyanate (**2,** 1 mmol) was added to the solution and further refluxed for 20 minutes. After the completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and poured onto excess of crushed ice to afford the corresponding imidazole-2-thione (**5**) as a solid which was filtered and recrystallized from distilled ethanol.

1, 3, 4-Triphenyl-1H-Imidazole-2(3H)-Thione **(5a)**

Obtained as a white solid; Mp.171-172 ºC. ^{1}H NMR (300 MHz, $CDCl_3$: δ 7.72 – 7.69 (m, 2H), 7.55 – 7.29 (m, 8H), 7.25 – 7.13 (m, 3H), 7.08 – 6.98 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.47, 138.04, 136.78, 131.46, 128.85, 128.83, 128.70, 128.48, 128.29,

128.20, 128.12, 127.69, 125.96, 116.10. Anal. Calc. for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53; S, 9.76. Found: C, 76.95; H, 4.90; N, 8.52; S, 9.75.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website

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[28] CCDC 1443331.

[29] CCDC 1433291.

Scheme 1. Sequential of the same components in the synthesis of different heterocycles (4 & 5)

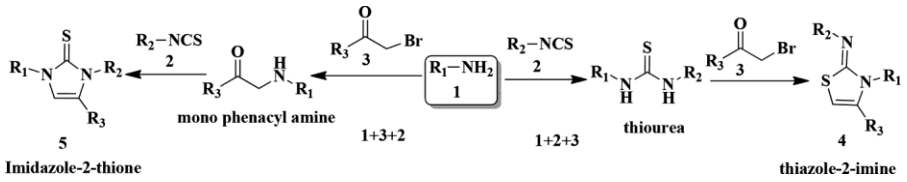
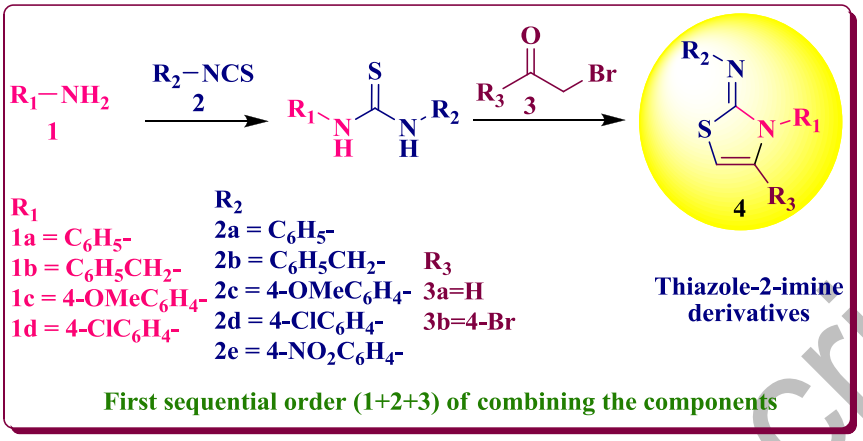
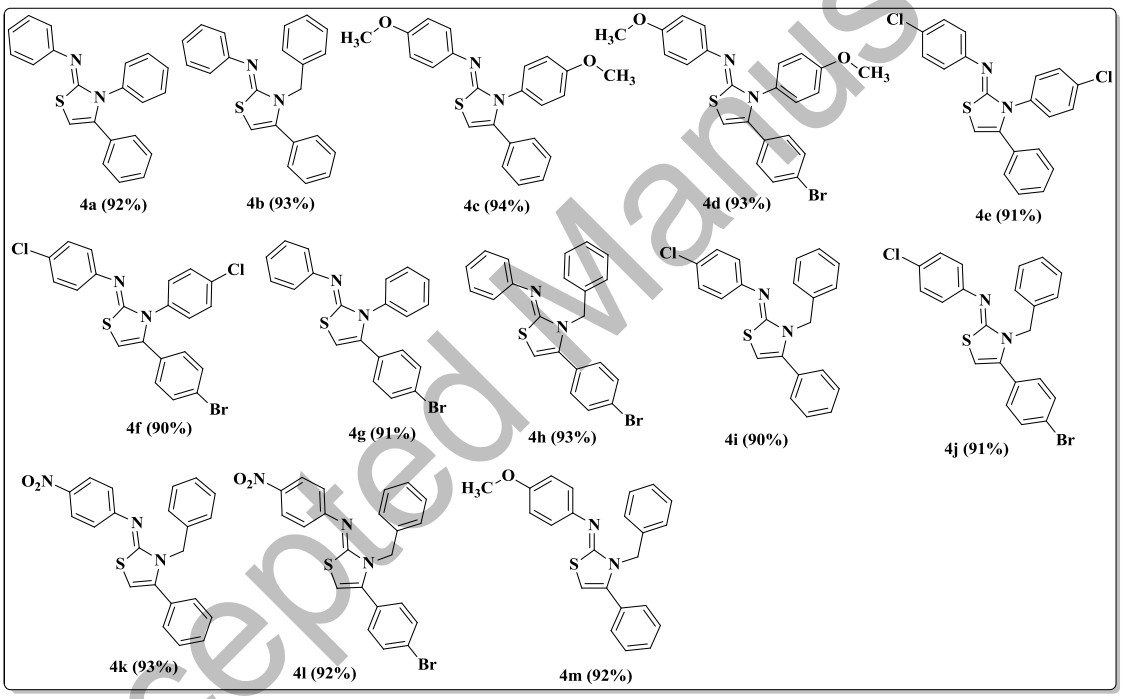


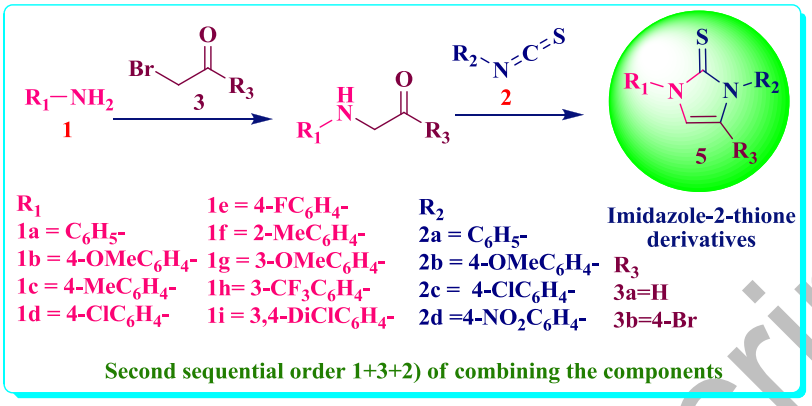
Table 1. One-pot three component synthesis of thiazole-2-imine derivatives (**4a-m**). [a]

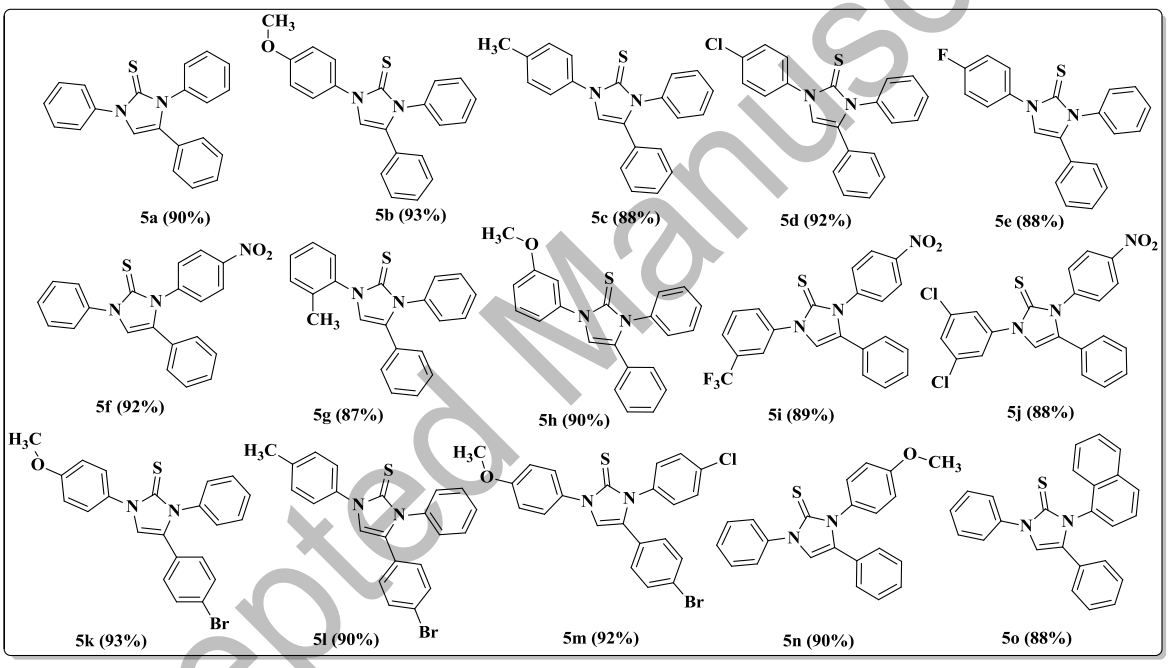




[a]Reaction conditions: To the amine (**1**, 1 mmol) in ethanol (3mL), aryl isothiocyanate (**2**, 1 mmol) was added followed by phenacyl bromide (**3**, 1 mmol) and the solution was refluxed for 30 minutes.

Table 2. One-pot three component synthesis of imidazole-2-thione derivatives (**5a-o**). [b]





[b]Reaction conditions: To the amine (**1**, 1 mmol) in ethanol (3mL), phenacyl bromide (**3,** 1 mmol) was added and refluxed for 30 minutes and then aryl isothiocyanate (**2,** 1 mmol) was added to the solution and further refluxed for 20 minutes.

Figure 1. X-ray crystal structure of the compound 4k[28]: Ellipsoid probability level 30%

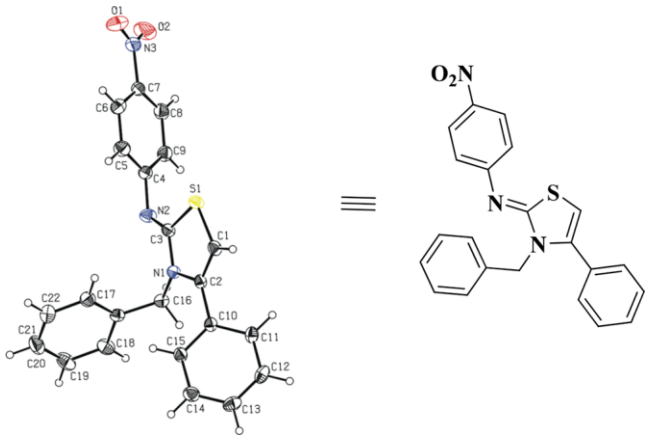


Figure 2. X-ray crystal structure of the compound 5k[29] : Ellipsoid probability level 30%