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Synthesis of Cinnoline Substituted Triazoles with Greener Procedures and Antibacterial Evaluation

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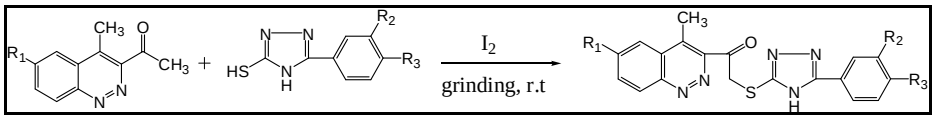
ABSTRACT

3-Acetyl-4-methyl-6-substituted-cinnolines have been condensed with 3-substituted-5-mercapto-1,2,4-triazoles using iodine crystals as catalyst by room temperature grinding to give 3-substituted-5-(4-methyl-6-substituted-cinnolin-3-yl)acylthio-1,2,4-triazoles. Synthesis of cinnoline-triazoles by grinding technique provides high yields and avoids additional use of deleterious organic solvents. The synthesized compounds have been characterized by spectral interpretations and their antibacterial potential has been described against diverse bacteria's.

Graphical Abstract



Keywords: 3-Substituted-5-mercapto-1,2,4-triazoles, 3-Acetyl-4-methyl-6-substituted-cinnolines, Iodine crystals, Grinding technique.

INTRODUCTION

Cinnolines and its fused derivatives constitute a versatile class of nitrogen based heterocyclic compounds possessing numerous therapeutic applications such as antimalarial [**1**], anti-molluscicidal [**2**], antitumor [**3**], human neutrophil elastase inhibitors [**4**], antithrombotic [**5**], antibacterial [**6**], LRRK2 kinase inhibitor [**7**], anti-inflammatory [**8**], antihypertensive [**9**], insecticidal [**10**], sedative [**11**] and antileukemic [**12**]. 1,2,4-Triazoles are have also attracted considerable attention because of their potential pharmacodynamic properties such as antibacterial [**13**], hypoglycemic [**14**], antiviral [**15**], antifungal [**16**], insecticidal [**17**], antitumor [**18**], anti-inflammatory [**19**] and CNS depressant [**20**]. Diverse pharmacological profile of cinnoline and triazole derivatives prompted us to explore the condensation reaction of varied triazoles with cinnolines and to envisage the antimicrobial potential of the synthesized compounds.

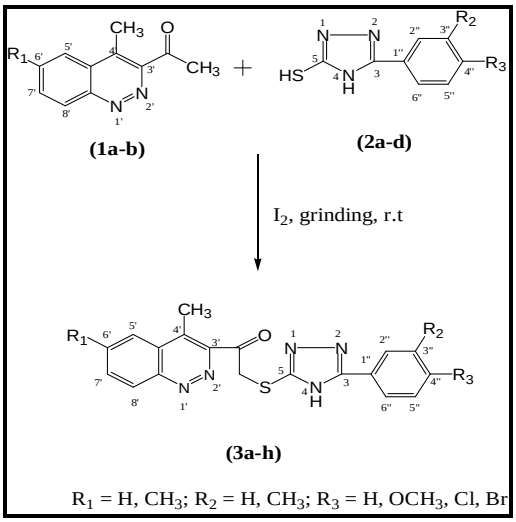
In recent years much emphasis is being laid on development of cleaner and greener synthetic methodologies in order to protect the environment. In reported methods bromoacetyl derivatives of cinnolines are generally used for fusion with various nitrogen heterocycles, but synthesis of bromoacetyl derivatives from acetyl derivatives requires use of corrosive molecular bromine. In the

present work, iodine being an effective and easily available catalyst for various organic transformations [21-23], is explored for condensation of acetyl derivative of cinnolines with 1,2,4-triazoles at room temperature under solvent free conditions.

MATERIALS AND METHODS

The necessary chemicals and reagents were obtained from Sigma-Aldrich. Perkin-Elmer 2400 CHN Elemental analyzer was used for chemical characterization, Perkin-Elmer Spectrophotometer for Infrared spectra and BrukerAvance II 400 MHz Spectrometer was used for proton NMR spectra.

General procedure for synthesis of 3-substituted-5-(4-methyl-6-substituted-cinnolin-3-yl)acyl thio-1,2,4-triazole: A mixture of 3-acetyl-4-methyl-6-substituted-cinnoline (2.0 mmol), 3-substituted-5-mercapto-1,2,4-triazole (2.0 mmol), I_2 (0.35 mmol) and 6 drops of rectified spirit was ground manually in porcelain mortar-pestle at room temperature for 6 min. The pasty mass thus formed was left in mortar. As indicated by TLC, the reaction was completed in 9 min. Crushed ice was added to the pasty mass and iodine present was neutralized with aqueous sodium thiosulphate solution (10%). The solid formed was filtered and recrystallization with DMF-C_2H_5OH (3:2).



Scheme 1. Synthesis of cinnoline triazoles.

Antibacterial evaluation: The synthesized cinnoline-triazoles were examined against diverse bacteria's i.e., *K. pneumoniae*, *E. coli*, *S. typhii*, *P. aeruginosa* and *S. aureus* by ditch diffusion method [24]. A two hour culture of bacterial strains grown on Peptone-water medium at 37°C was taken as test organism. The culture medium chosen was Muller-Hilton agar medium, Ciprofloxacin as standard antibacterial drug and Dimethylformamide acts as solvent control.

RESULTS AND DISCUSSION

With the ever-increasing problem of depletion of natural resources and environmental degradation, the classical research is shifted towards environmentally benign and sustainable technologies. Use of noxious chemicals and carbon based organic solvents is also reduced due to environmental pollution and health disorders. In the present investigation, an attempt has been made to synthesize therapeutically significant heterocyclic compounds at room temperature with negligible use of deleterious organic solvents. 3-Acetyl-4-methyl-6-substituted-cinnolines [6] have been condensed with 3-substituted-5-mercapto-1,2,4-triazoles [25] using iodine crystals as catalyst to give cinnoline substituted triazoles (3a-h) (Scheme 1). The cinnoline-triazoles are formed in high yields and are well characterized by elemental analysis and spectral interpretations. The results have been compiled in table 1, 2 and 3.

Table 1. Synthesis of cinnoline-triazoles

Compound	R_1	R_2	R_3	M.pt. (°C)	Yield (%)	Time$^{(x+y)}$ (min)
3a	H	H	OCH_3	188-89	87	6+9
3b	H	CH_3	H	180-81	80	6+9
3c	H	H	Cl	196-97	81	6+9
3d	H	H	Br	190-91	83	6+9
3e	CH_3	H	OCH_3	193-94	82	6+9
3f	CH_3	CH_3	H	174-75	80	6+9
3g	CH_3	H	Cl	198-99	84	6+9
3h	CH_3	H	Br	180-81	84	6+9

x: time of grinding, y: time for which reaction mixture was left at room temperature

Table 2. Elemental analysis of cinnoline-triazoles

Compound	Mol. Formula	C %		H %		N %	
		Calc.	Found	Calc.	Found	Calc.	Found
3a	$C_{20}H_{17}N_5O_2S$	61.38	61.42	4.34	4.46	17.90	17.98
3b	$C_{20}H_{17}N_5OS$	64.00	64.08	4.53	4.25	18.66	18.51
3c	$C_{19}H_{14}N_5OSCl$	57.64	57.70	3.53	3.68	17.69	17.85
3d	$C_{19}H_{14}N_5OSBr$	51.82	51.98	3.18	3.26	15.91	15.80
3e	$C_{21}H_{19}N_5O_2S$	62.22	62.36	4.69	4.75	17.28	17.12
3f	$C_{21}H_{19}N_5OS$	64.78	64.62	4.88	4.68	17.99	17.88
3g	$C_{20}H_{16}N_5OSCl$	58.60	58.78	3.90	3.97	17.09	17.31
3h	$C_{20}H_{16}N_5OSBr$	52.87	52.94	3.52	3.67	15.42	15.60

Table 3. IR and NMR data of cinnoline-triazoles

Compound	IR (KBr) Str. in cm^{-1}				^{1}H NMR ($CDCl_3$, 400MHz): δ
	-N-H	C=O	C=N-	C-S	
3a	3448	1660	1612	728	7.89 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.80-7.55 (m, 4H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H and $C_{8'}$-H), 7.51(s, 1H, N_4-H), 6.94 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.69 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3).
3b	3464	1673	1619	743	7.88 (s, 1H, $C_{2''}$-H), 7.77-7.50 (m, 7H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H, $C_{8'}$-H, $C_{4''}$-H, $C_{5''}$-H and $C_{6''}$-H), 7.47 (s, 1H, N_4-H), 4.72 (s, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).
3c	3425	1654	1614	727	7.85 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.81-7.51 (m, 4H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H and $C_{8'}$-H), 7.49 (s, 1H, N_4-H), 6.91 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.57 (s, 2H, CH_2), 2.47 (s, 3H, CH_3).
3d	3488	1652	1611	740	7.88 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.76-7.50 (m, 4H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H and $C_{8'}$-H), 7.47 (s, 1H, N_4-H), 6.85 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.50 (s, 2H, CH_2), 2.35 (s, 3H, CH_3).
3e	3445	1772	1621	725	7.87 (s, 1H, $C_{5'}$-H), 7.80 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.74-7.52 (m, 2H, $C_{7'}$-H and $C_{8'}$-H), 7.45 (s, 1H, N_4-H), 6.82 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.70 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 2.28 (s, 3H, CH_3).
3f	3431	1678	1635	755	7.88 (s, 1H, $C_{2''}$-H), 7.82 (s, 1H, $C_{5''}$-H), 7.80-7.50 (m, 5H, $C_{7'}$-H, $C_{8'}$-H, $C_{4''}$-H, $C_{5''}$-H and $C_{6''}$-H), 7.46 (s, 1H, N_4-H), 4.80 (s, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.26 (s, 3H, CH_3).
3g	3465	1650	1620	741	7.85 (s, 1H, $C_{5'}$-H), 7.82 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.64-7.57 (m, 2H, $C_{7'}$-H and $C_{8'}$-H), 7.46 (s, 1H, N_4-H), 6.81 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.65 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.25 (s, 3H, CH_3).
3h	3450	1661	1623	721	7.87 (s, 1H, $C_{5'}$-H), 7.83 (d, 2H, J = 8.8 Hz, $C_{2''}$-H and $C_{6''}$-H), 7.67-7.54 (m, 2H, $C_{7'}$-H and $C_{8'}$-H), 7.51 (s, 1H, N_4-H), 6.84 (d, 2H, J = 8.8 Hz, $C_{3''}$-H and $C_{5''}$-H), 4.48 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).

Antibacterial activity: By calculating the diameter of zone of the inhibition the antibacterial potential is evaluated and the optimum results were obtained at 10 ppm concentration. All the compounds 3a-h shows moderate to strong activity against *K. pneumoniae*, *E. coli*, *S. typhii*, *P. aeruginosa.* Against *S. aureus*, compound 3a**,** 3b, 3c and 3f showed moderate activity. The results are illustrated in table 4.

Table 4. Antibacterial activity data of cinnoline-triazoles

Compound	Diameter of zone of inhibition (mm)									
	K. pneumonia		*E. coli*		*S. typhii*		*P. aeruginosa*		*S. aureus*	
	10 ppm	100 ppm	10 ppm	100 ppm	10 ppm	100 ppm	10 ppm	100 ppm	10 ppm	100 ppm
3a	13	11	14	12	12	10	14	12	12	10
3b	15	13	16	14	11	11	12	11	11	10
3c	12	10	15	12	13	10	12	10	13	11
3d	13	11	14	11	12	10	14	10	-	-
3e	12	10	13	12	-	-	12	11	-	-
3f	14	12	16	13	13	11	11	9	12	10
3g	12	10	15	11	14	10	13	10	-	-
3h	-	-	14	13	13	10	13	11	-	-
Ciprofloxacin	20	20	20	20	20	20	20	20	20	20

APPLICATION

The synthesized cinnoline-triazoles possess antibacterial potential against different bacteria's and can be further used in therapeutic investigations.

CONCLUSION

In conclusion, we have efficiently synthesized cinnoline-triazoles under eco-friendly conditions. Shorter reaction times, mild conditions, high yields, operational simplicity and solvent free conditions are the merits of this protocol.

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