iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 10 **Issue:** I **Month of publication:** January 2022

DOI: https://doi.org/10.22214/ijraset.2022.39749

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 10 Issue I Jan 2022- Available at www.ijraset.com

Iodic Acid Catalyzed Efficient Synthesis of 2-Amino Thiazoles

Praveen V. Shitre[1], Ganesh V Shitre[2], Omprakash S. Chavan[3], Madhav J. Hebade[4]
[1]*Assistant Professor, Department of Chemistry, Yeshwantrao Chavan Mahavidyalaya Sillod, Aurangabad, (Maharashtra), India*
[2]*Assistant Professor, Department of Chemistry, Vaishnavi Mahavidyalaya Wadwani, Dist. Beed, (Maharashtra), India*
[3, 4]*P.G., Dept. of Chemistry, Badrinarayan Barwale College, Jalna, MS-431213*

Abstract: ***This study describes a straightforward, efficient, one-step, environmentally friendly synthesis of 2-aminothiazoles. This green procedure was catalyzed using an Iodic Acid catalyst and PEG-400 as green solvent. The synthesized compounds were characterized by*** ^{1}***H NMR,*** ^{13}***C NMR and HRMS analyses.***
Keywords: 2-aminothiazoles, Iodic acid, PEG-400: H_2O

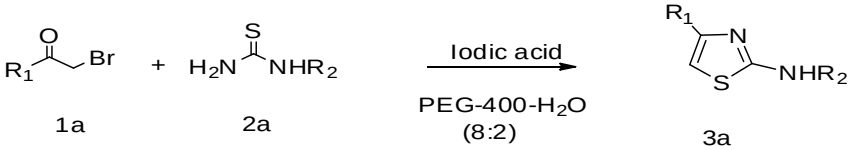
I. INTRODUCTION

One of the most difficult tasks for researchers in recent decades has been to develop the most efficient methodology for organic synthesis, which can be realized by employing innovative research that comprehensively meets the requirements of atom economy, step economy, and avoidance of any hazardous chemicals. One of the most effective techniques will be those that address the aims of green chemistry. The 2-aminothiazole ring system is gaining popularity as its derivatives have been discovered to exhibit a diverse range of biological activities. This structure has been used in the treatment of allergies (1), hypertension (2), inflammation (3), schizophrenia (4), and bacterial (5) and HIV (6) infections. It has recently been used to treat pain (7), as fibrinogen receptor antagonists with antithrombotic action (8), as bacterial DNA gyrase inhibitors (9), and in the creation of cyclin-dependent kinase inhibitors (10). Therefore, much attention has been paid to the synthesis of 2-aminothiazoles, for which the general approaches include condensation of a-bromoketone with thiourea,(11) the reaction of a-thiocyanato carbonyl compounds with aromatic or aliphatic amine hydrochlorides,(12) treatment of stylene and thiourea with NBS (13) and condensation of aromatic ketone and thiourea with solid supported catalyst or heterogeneous catalyst. Tandem, multicomponent, and one-pot reactions have received a lot of attention in recent years as strong and effective synthetic tools in synthetic chemistry and drug development. These reactions have been employed in numerous chemical transformations because to their atom-economy, which reduces the number of processes while conserving reagents, energy, time, and laborious. (14) Due to the significance of 2-aminothiazoles and their derivatives, various techniques for their synthesis have been documented in the literature (15). Some of these processes have significant flaws, such as poor yield, high reaction temperatures, the use of costly, moisture and air-sensitive catalysts, a time-consuming purification process, and toxic solvents. These procedures also produce waste solvents and catalysts, which must be collected, handled, and disposed of. Despite the variety of techniques available, there is always a need to seek for improved catalysts in terms of toxicity, handling, availability, economic viability, and operational simplicity. However, development of novel environmentally benign approaches for the synthesis of thiazoles, is highly desirable.

II. RESULTS AND DISCUSSION

A. Chemistry

We report herein, a mild and efficient protocol for the synthesis of 2- amino thiazole derivatives. To the best of our knowledge there are no reports on the synthesis of thiazoles from phenacyl bromides and thiourea catalysed by iodic acid in PEG-400-H_2O (Schemes 1). Keeping the above observations in mind and motivated from our previous work here, first time iodic acid backed strategy for the reaction between phenacyl bromides and thiourea have been reported for obtaining high yields of 2-amino thiazoles scaffolds (**3a-k**).



1a 2a 3a

Scheme 1. Synthesis of 2-Amino thiazoles (3a-k).

In the present work, **1a** and **2a** have been reacted with using iodic acid as reusable catalyst. Attempts were made to accomplish precise reaction conditions for the reaction. In search of specific reaction conditions, the model reaction has been carried out by varying solvents. Firstly, we accomplished reaction between **1a** and **2a** as a model reaction in the presence iodic acid to obtain **3a**. This model reaction was performed under identical condition in different solvents. The screening results of the model reaction run in different solvents at room temp in the presence of iodic acid are noted in **Table 1, entry 1-11.** Among the screened solvents, PEG-400:H_2O was found to be the utmost solvent to afford product **3a.**

Table 1. Screening of the solvent for synthesis of compound 3a.[a]

Entries	Solvent	Time (Min)	Yields %
1	DMF	50	40
2	PEG-400-water	120	97
3	MeOH	90	75
4	DMSO	75	73
5	1,4-Dioxane	65	87
6	$CHCl_3$	90	65
7	EtOH	110	90
8	THF	80	72
9	Toluene	90	80
10	CH_3CN	85	82
11	DCM	110	76

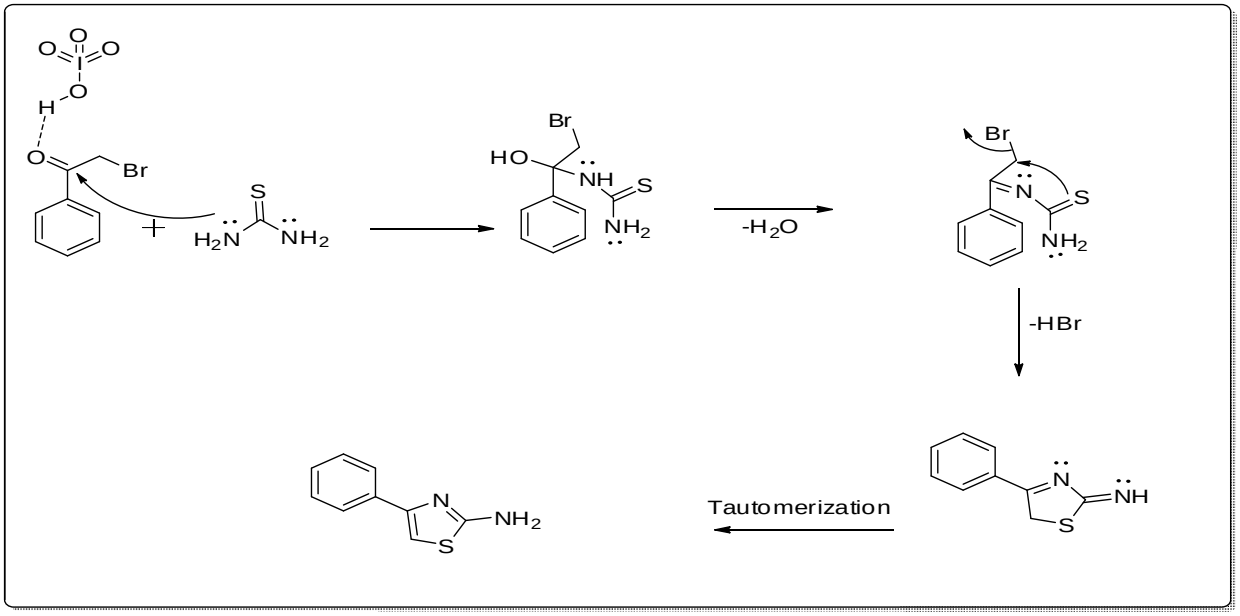
[a]**Reaction conditions:** phenacyl bromide **(1a)** (0.001 mol), Thiourea (**2a**) (0.001 mol), Iodic acid (0.001), solvent (10 mL), at RT, [b]Isolated yields.

Table:2. Iodic acid promoted synthesis of 2-aminothiazoles.

Entry	R1	R2	Product	Time	M.P.	Yield
1			**3a**	40	**150–151**	97
2			**3b**	35	**136–137**	96
3			**3c**	30	**204–205**	93
4			**3d**	40	**180–181**	92
5			**3e**	30	**165–167**	94
6			**3f**	35	**143–144**	95
7			**3g**	35	**176–177**	91

8			**3h**	40	**152–153**	93
9			**3i**	40	**136–137**	94
10			**3j**	35	**170–171**	90
11			**3k**	30	**174–176**	92

The plausible mechanism for synthesis of 2-aminothiazoles is shown in **Figure 1**



III. EXPERIMENTAL

A. Materials and Methods

All chemicals were purchased from Sigma-Aldrich and were used as such. All reactions and purity of 2-aminothiazoles were monitored by thin-layer chromatography (TLC) using aluminium plates coated with silica gel F254 plates (Merck) using 40% ethyl acetate and 60% petroleum ether as an eluent. The spots were detected either under UV light. Melting points were determined using an open capillary method and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710. ^{1}H NMR and ^{13}C NMR were recorded on Bruker 400 MHz, using TMS as an internal standard and mass spectra on a V.G. auto spectrometer using ESI techniques.

B. General Procedure for the Synthesis of 2-Aminothiazoles

In a 100 ml round-bottomed flask was filled with phenacyl bromide (1 mmol), thiourea (1 mmol) and iodic acid (1mmol). The mixture was then stirred at room temperature until the reaction was complete. The reaction was monitored by TLC. After completion of reaction 50 ml of ice-cold water was added. The solid 2-aminothiazole product that separated out was filtered, then washed with water and dried. The crude product, thus obtained was subjected for recrystallization using an ethanol. The structures of all products were confirmed on the basis of spectral analysis IR, ^{1}HNMR,^{13}CNMR, mass spectral data and melting point.

C. Spectral and Analytical Data for synthesized Compounds 3a–k

1) 2-Amino-4-phenylthiazole (3a)

IR (cm^{-1}, KBr): 3400, 3260, 1640, 1462, 1377, 765, 653; ^{1}H NMR (MeOH, 300 MHz): δ 3.96 (s, NH_2), 6.7 (s, 1H), 7.22 (m, 1H, Ar–H), 7.32 (m, 2H, Ar–H), 7.48 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.4, 127.0, 129.1, 128.5, 150.8, 173.2; HRMS; *m/z* 176.2415 *(M+)*; $C_9H_8N_2S$: calcd. C, 61.33; H, 4.57; N, 15.8; found C, 61.24; H, 4.61; N, 15.7.

2) 2-Phenylamino-4-phenylthiazole (3b)

IR (cm^{-1}, KBr): 3318, 1614, 1463, 1377, 770, 694; ^{1}H NMR (MeOH, 300 MHz): δ 4.0 (s, NH_2), 6.7 (s, 1H), 7.27 (m, 1H, Ar–H), 7.34 (m, 1H, Ar–H), 7.52 (m, 2H, Ar–H), 6.46 (m, 2H, Ar–H), 7.01 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.4, 115.1, 118.5, 127.2, 128.5, 129.0, 129.3, 136.5, 146.7, 173.2; HRMS; *m/z* 252.343 *(M+)*; $C_{15}H_{12}N_2S$: calcd. C, 71.3; H, 4.8; N, 11.1; found C, 71.1; H, 4.8; N, 11.2.

3) 2-Amino-4 (4_-methoxyphenyl) thiazole (3c)

IR (cm^{-1}, KBr): 3382, 3269, 1631, 1461, 1259, 850, 723; ^{1}H NMR (MeOH, 300 MHz): δ 3.77 (s, NH_2), 6.74 (s, 1H), 3.73 (s, –OCH3), 6.88 (m, 2H, Ar–H), 7.72 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 54.3, 103.4, 114.2, 128.8, 150.2, 162.2, 173.2; HRMS; *m/z* 206.268 *(M+)*; $C_{10}H_{10}N_2SO$: calcd. C, 58.2; H, 4.8; N, 13.6; found C, 58.4; H, 4.7; N, 13.7.

4) 2-Phenylamino-4 (4_-methoxyphenyl) thiazole (3d)

IR (cm^{-1}, KBr): 3410, 1640, 1461, 1370, 762, 690; ^{1}H NMR(MeOH, 300 MHz): δ 3.82 (s, NH_2), 6.64 (s, 1H), 6.94 (m, 1H, Ar–H), 7.85 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H), 7.2 (m, 1H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 56.0, 103.2, 115.2, 115.3, 118.5, 129.2, 129.3, 144.7, 156.8, 173.2; HRMS; *m/z* 282.365 *(M+)*; $C_{16}H_{14}N_2SO$: calcd. C, 68.1; H, 4.9; N, 9.9; found C, 68.2; H, 4.9; N, 9.7.

5) 2-Amino-4 (4_-bromophenyl) thiazole (3e)

IR (cm^{-1}, KBr): 3372, 3272, 1632, 1458, 1372, 764, 672; ^{1}H NMR (MeOH, 300 MHz): δ 4.0 (s, NH_2), 6.6 (s, 1H), 7.47 (m, 2H, Ar–H), 7.52 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 101.2, 124.2, 129.2, 132.3, 136.5, 152.8, 173.2; HRMS; *m/z* 255.267 *(M+)*; $C_9H_7N_2SBr$: calcd. C, 42.3; H, 2.7; N, 11.0; found C, 42.2; H, 2.5; N, 11.2.

6) 2-Phenylamino-4 (4_-bromophenyl)-thiazole (3f)

IR (cm^{-1}, KBr): 3340, 1617, 1470, 1370, 762, 680; ^{1}H NMR (MeOH, 300 MHz): δ 4.1 (s, NH_2), 6.7 (s, 1H), 7.23 (m, 2H, Ar–H), 7.53 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.7 (m, 1H, Ar–H), 7.2(m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.2, 114.2, 118.5, 123.1, 128.3, 129.2, 132.4, 137.2, 147.2, 150.8, 174.2; HRMS; *m/z* 331.362 *(M+)*; $C_{15}H_{11}N_2SBr$: calcd. C, 54.3; H, 3.3; N, 8.5; found C, 54.4; H, 3.1; N, 8.2.

7) 2-Amino-4 (4_-chlorophenyl) thiazole (3g)

IR (cm^{-1}, KBr): 3383, 3266, 1627, 1494, 1395, 745, 657; ^{1}H NMR (MeOH, 300 MHz): δ 4.2 (s, NH_2), 6.63 (s, 1H), 7.28 (m, 2H, Ar–H), 7.52 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 102.3, 128.3, 129.8, 133.2, 134.6, 150.2, 173.2; HRMS; *m/z* 210.814 *(M+)*; $C_9H_7N_2SCI$: calcd. C, 51.31; H, 3.35; N, 13.30; found C, 51.33; H, 3.32; N, 13.32.

8) 2-Phenylamino-4 (4_-chlorophenyl) thiazole (3h)

IR (cm^{-1}, KBr): 3400, 1640, 1462, 1377, 765, 653; ^{1}H NMR(MeOH, 300 MHz): δ 3.96 (s, NH_2), 6.7 (s, 1H), 7.22 (m, 1H, Ar–H), 7.52 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H), 7.2 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 104.2, 115.2, 118.5, 128.3, 129.4, 133.8, 134.6, 146.7, 150.8, 173.2; HRMS; *m/z* 176.2415 *(M+)*; $C_9H_8N_2S$: calcd. C, 61.33; H, 4.57; N, 15.8; found C, 61.2; H, 4.4; N, 15.5.

9) 2-Amino-4 (4_-methylphenyl) thiazole (3i)

IR (cm^{-1}, KBr): 3412, 3264, 1632, 1470, 1362, 764, 682; ^{1}H NMR (MeOH, 300 MHz): δ 3.8 (s, NH_2), 6.38 (s, 1H), 2.35 (s, 1H), 7.14 (m, 1H, Ar–H), 7.32 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 21.1, 102.3, 126.9, 129.2, 134.2, 137.7, 173.2; HRMS; *m/z* 190.326 *(M+)*; $C_{10}H_{10}N_2S$: calcd. C, 63.1; H, 5.3; N, 14.7; found C, 63.3; H, 5.1; N, 14.7.

10) 2-Phenylamino-4 (4_-methylphenyl) thiazole (3j)

IR (cm^{-1}, KBr): 3352, 1614, 1462, 1373, 772, 678; ^{1}H NMR (MeOH, 300 MHz): δ 4.2 (s, NH_2),6.8 (s, 1H), 2.34 (s, 3H, CH3), 7.12 (m, 2H, Ar–H), 7.38 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H),6.62 (m, 1H, Ar–H), 7.1 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 21.1, 102.3, 115.1, 118.3,127.1, 129.3, 134.2, 137.7, 146.7, 173.2; HRMS; *m/z* 266.494 *(*M+*)*; $C_{16}H_{14}N_2S$: calcd. C, 72.1; H, 5.3; N, 10.6; found C, 72.1; H, 5.4; N, 10.3.

11) 2-(1_-Naphthyl)-amino-4(4__-bromophenyl) thiazole (3k)

White solid. IR (KBr) *v*max cm^{-1}: 3054, 1544, 1397, 1105, 767, 680. ^{1}H NMR (DMSO-d6, 400 MHz,): δ = 7.02 (s, 1H, −CH), 10.14 (br s, 1H, −NH), 7.45−7.74 (m, 11H, Ar-H).^{13}C NMR (DMSO-*d*6, 75 MHz,): 102.84, 121.80, 123.87, 125.41, 125.56, 125.81, 127.25, 127.89, 131.13, 146.76, 166.50. *m/z* (ESI-MS, HRMS): 379.965 (M+). $C_9H_{13}BrN_2S$: Calcd. C, 59.85; H, 3.44; N, 7.35; found C, 59.67; H, 3.27; N, 7.22.

IV. CONCLUSION

In conclusion, we have developed a mild, efficient and eco-friendly protocol for synthesis of 2- aminothiazole (3 a-k) from substituted phenyl bromide & thiourea using iodic acid as catalyst & PEG 400 and water as a solvent. The key feature of the protocol involve simple reaction condition no side reaction and product formation in high yield. In present protocol is an alternative to the conventional process for the synthesis of 2- amino thiazole.

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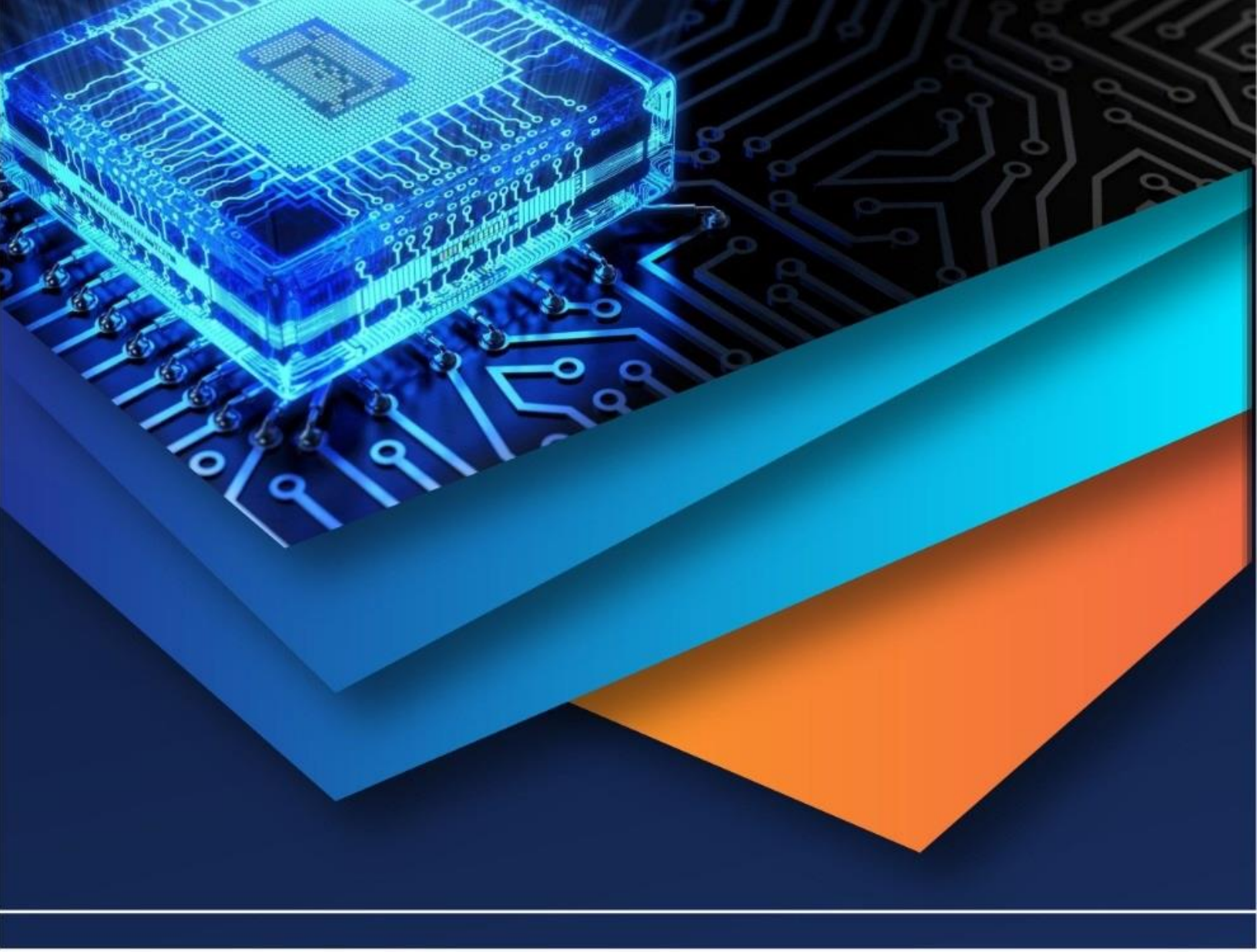

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