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Research Note

An efficient synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives by a three-component reaction of 5-aminotetrazole, arylaldehydes, and dimedone

A. Hassankhani* **and E. Mosaddegh**

Department of New Materials, Institute of Science and High Technology and Environmental Sciences, Graduate University of Advanced Technology, Kerman, P.O. Box 76315-117, Iran.

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Tetrahydrotetrazolo[1,5-*a*]quinazoline;
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Solvent-free.

Abstract. A series of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives were prepared by the three-component condensation reaction of 5-aminotetrazole (5-AT), benzaldehydes, and dimedone, in the presence of *p*-toluenesulfonic acid (*p*-TSA) as a solid acid catalyst, under solvent-free conditions. This protocol provides a simple one-step procedure with the advantages of having easy work-up, mild reaction conditions, and being environmentally benign.

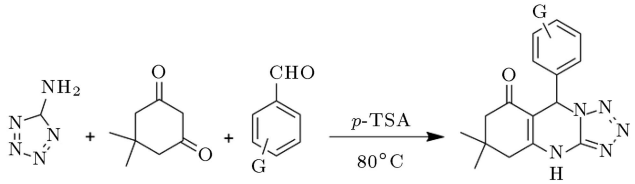
1. Introduction

Multi-Component Reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry due to their valued features, such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, the purification of products resulting from MCRs is also simple, since all organic reagents employed are consumed and incorporated into the target compound [1,2]. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules [3-10].

Tetrazoloquinazolinones or tetrazolopyrimidines (TPs), nitrogen-bridgehead fused heterocycles containing a tetrazole ring, are a common structural motif in pharmacologically important molecules, with activities spanning a diverse range of targets [11,12]. These compounds are reported to have been used in the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid cancer, hypothyroidism, depression, glaucoma, cardiac arrhythmias, and congestive heart failure [13-18]. The development of simple synthetic methods for these derivatives is, therefore, important in organic synthesis.

A literature survey has revealed that there are only a limited number of publications devoted to the synthesis of azolopyrimidines, especially tetrahydrotetrazolo[1,5-*a*]quinazoline [19-34]. To date, the most widespread pathway to these structures has involved the initial synthesis of α,β-unsaturated carbonyl skeletons [21-31], such as chalcones, Mannich bases or arylidenepyruvic acids in rather poor yields, followed by further cyclocondensation with 5-AT. In continuation of our efforts to develop new methods [35] and due to the biological activity of a sig-

*. *Corresponding author. Tel.: +98 3426226617; Fax: +98 3426226611-12*
E-mail addresses: hassankhani_a@yahoo.com (A. Hassankhani); emosaddegh@gmail.com (E. Mosaddegh)



Scheme 1. One-pot synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives.

nificant number of tetrazoloquinazolinones and our interest in MCRs [36], we have decided to explore the possibility of synthesizing tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives via a novel, one-pot, three-component condensation of 5-AT, aromatic aldehydes, and dimedone under solvent-free conditions using *p*-TSA as a catalyst (Scheme 1).

2. Experimental

2.1. Materials and instruments

Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Melting points were determined by a Gallenkamp melting point and are not corrected. Thin-Layer Chromatography (TLC) on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the progress of reactions. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400-MHz spectrometers at 400 and 100 MHz, respectively.

2.2. General procedure for the preparation of tetrahydrotetrazolo[1,5-a]quinazoline (4a − j)

A mixture of dimedone (0.28 g, 2 mmol), 5-aminotetrazole monohydrate (0.210 g, 2 mmol), benzaldehyde derivatives (2 mmol), and *p*-TsOH.H_2O (0.076 g, 20 mol%) was heated at 80°C for 5-10 min (TLC). After cooling, the reaction mixture was washed with water (10 mL) and the residue recrystallized from ethanol to afford the pure products.

All products were characterized by ^{1}HNMR and ^{13}CNMR, and identified by comparison of the spectral data and melting points with those reported in the literature [19,20].

2.3. NMR spectral data of the products

4*a*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.00 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.13-2.27 (m, 2H, CH_2), 2.61 (s, 2H, CH_2), 6.61 (s, 1H, 9-CH), 7.29-7.36 (m, 5H, ArH), 11.65 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.47, 28.75, 32.79, 50.28, 57.93, 106.13, 127.64, 128.82, 129.07, 140.94, 148.93, 150.97, 193.50.

4*b*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12-2.26 (m, 2H, CH_2), 2.60 (s, 2H, CH_2), 6.62 (s, 1H, 9-CH), 7.27 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 11.68 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.57, 28.64, 32.81, 50.26, 57.42, 105.73, 122.05, 129.98, 132.00, 140.28, 148.85, 151.16, 193.54.

4*c*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 0.99 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.09-2.26 (m, 2H, CH_2), 2.62 (s, 2H, CH_2), 6.79 (s, 1H, 9-CH), 7.62 (d, J = 8.8 Hz, 2H, ArH), 8.19 (d, J = 8.8 Hz, 2H, ArH), 11.81 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.61, 28.55, 32.84, 50.18, 57.40, 124.28, 129.32, 147.54, 147.77, 148.89, 151.58, 193.58.

4*d*: pale green powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.06-2.20 (m, 2H, CH_2), 2.58 (s, 2H, CH_2), 7.22 (s, 1H, 9-CH), 7.36 (d, J = 7.6 Hz, 1H, ArH), 7.55 (t, 1H, J = 7.6 Hz, ArH), 7.66 (t, J = 7.6 Hz, 1H, ArH), 7.93 (d, J = 9.2 Hz, 1H, ArH), 11.83 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.53, 28.36, 32.72, 49.85, 53.25, 105.55, 124.66, 129.89, 130.09, 133.89, 134.35, 148.75, 148.95, 151.44, 193.45.

4*e*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.10-2.24 (m, 2H, CH_2), 2.59 (s, 2H, CH_2), 6.91 (s, 1H, 9-CH), 7.43-7.50 (m, 2H, ArH), 7.62 (s, 1H, ArH), 11.77 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.56, 28.64, 32.73, 50.24, 104.71, 128.13, 129.77, 133.66, 134.31, 149.01, 151.87, 193.49.

4*f*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.13-2.26 (m, 2H, CH_2), 2.65 (s, 2H, CH_2), 6.63 (s, 1H, 9-CH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.40 (*d*, J = 8.8 Hz, 2H, ArH), 11.68 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.57, 28.63, 32.81, 50.25, 57.34, 105.76, 129.08, 129.67, 133.43, 139.88, 148.85, 151.16, 193.55.

4*g*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.03 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.10-2.25 (m, 2H, CH_2), 2.60 (s, 2H, CH_2), 6.92 (s, 1H, 9-CH), 7.32-7.34 (m, 2H, ArH), 7.43-7.45 (m, 2H, ArH), 11.73 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.48, 28.73, 32.72, 50.27, 105.07, 127.94, 130.36, 130.61, 132.65, 137.42, 149.04, 151.65, 193.44.

4*h*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.14-2.28 (m, 2H, CH_2), 2.69 (s, 2H, CH_2), 6.85 (s, 1H, 9-CH), 7.65 (t, J = 8 Hz, 1H, ArH), 7.79 (d, J = 7.6 Hz, 1H, ArH), 8.17 (*d*, J = 8 Hz, 1H, ArH), 8.23 (s, 1H, ArH), 11.79 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) δ = 27.51, 28.63, 32.85, 50.19, 57.32, 105.23, 122.65, 123.86, 130.85, 134.44, 142.72, 148.22, 148.85, 151.76, 193.64.

4*i*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) δ = 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.12-2.26 (m, 2H, CH_2), 2.60 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 6.56 (s, 1H, 9-CH), 6.88 (d, J = 8.8 Hz, 2H, ArH), 7.22 (d, J = 8.8 Hz, 2H, ArH), 11.59 (s, 1H, NH); ^{13}C NMR (100

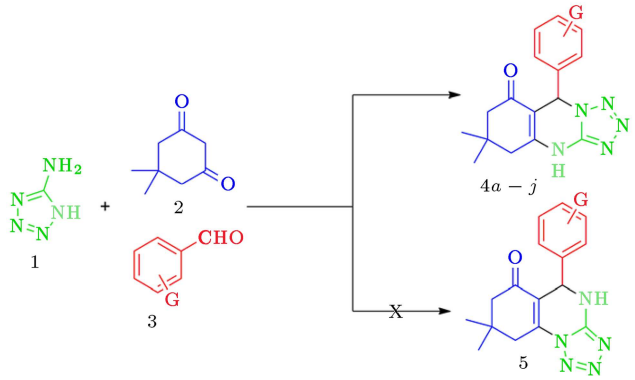
MHz, d6-DMSO) $\delta = 27.46, 28.80, 32.76, 50.32, 55.57, 57.39, 106.28, 114.37, 128.88, 133.20, 148.86, 150.72, 159.59, 193.49$.

4*j*: white powder; ^{1}H NMR (400 MHz, d6-DMSO) $\delta = 1.12$ (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.31 (s, 2H, CH_2), 2.67-2.78 (m, 2H, CH_2), 6.71 (s, 1H, 9-CH), 7.13 (d, $J = 8$ Hz, 2H, ArH), 7.23 (d, $J = 8$ Hz, 2H, ArH), 11.47 (s, 1H, NH); ^{13}C NMR (100 MHz, d6-DMSO) $\delta = 21.15, 27.54, 28.84, 32.90, 40.80, 50.49, 58.03, 107.60, 127.02, 129.58, 136.34, 138.84, 148.80, 149.05, 193.75$.

3. Results and discussion

To develop optimum conditions, first, the effect of temperature on the rate of the reaction was studied for the preparation of tetrahydrotetrazolo[1,5-*a*]quinazoline. At 80°C, the reaction proceeded to completion very rapidly. A decrease in temperature leads to a decrease in product yield and rate of reaction. It was observed that the reaction did not proceed at room temperature. Next, the optimum amount of *p*-TSA was evaluated. The highest yield was obtained with 20 mol% of the catalyst. A further increase in the amount of *p*-TSA up to 40 mol% had no significant effect on the product yield or reaction time. The generality of this reaction was examined using various substituted benzaldehydes. In all cases, the reactions gave the corresponding products in good to excellent yields and in short reaction times (Table 1).

The presence of a third nucleophilic center in the 5-amino-1*H*-tetrazole **1** (5-AT) could lead to the formation of products **4** or **5** (Scheme 2). The reaction showed a high regioselectivity. In all cases, only a sole regioisomer **4** was obtained in good yields (81-91%) (Only one product, tetrahydrotetrazolo[1,5-*a*]quinazoline **4a – j**) (Table 1).



Scheme 2. The regioselectivity of the reaction.

The structures of all compounds were determined on the basis of their analytical techniques, IR, ^{1}H NMR and ^{13}C NMR, which agree with the proposed structures [19,20]. It is interesting to note that the aliphatic aldehydes did not produce any desired products.

There are no established mechanisms for the formation of tetrahydrotetrazolo[1,5-*a*]quinazoline; a reasonable possibility is shown in Scheme 3. The reaction presumably proceeds via an initial reaction between *p*-TSA and 5-AT **1** to give the 5-amino-1H-tetrazoleium salt **6**. Next, Michael addition of compound **7** to benzylidene compound **8**, itself produced by Knoevenagel condensation of aldehyde **3** and dimedone **2**, gives intermediate **9**. Elimination of one proton from the imino group results in compound **10**. Finally, the cyclization of **11** results in the condensed ring system, **4a – j** (Scheme 3).

The reusability of the catalyst was examined in the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline

Table 1. *p*-TSA catalyzed the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives through three-component reaction.

Entry	Ar	Time (min)	Yield (%)[a]	TON[b]	TOF[c]	Melting point (°C)	Reported melting point[ref] (°C)
4*a*	C_6H_5	5	81	4.05	48.6	> 270	> 270[19]
4*b*	4-Br-C_6H_4	6	91	4.55	45.5	250-253	246-249[19]
4*c*	4-O_2N-C_6H_4	9	90	4.5	30	248-250	248-249[20]
4*d*	2-O_2N-C_6H_4	7	82	4.1	35.14	262-264	261-263[19]
4*e*	2,4-Cl_2-C_6H_3	10	89	4.45	26.7	> 270	> 270[19]
4*f*	4-Cl-C_6H_4	6	88	4.4	44	255-257	254-256[19]
4*g*	2-Cl-C_6H_4	5	86	4.3	51.6	> 270	> 270[19]
4*h*	3-O_2N-C_6H_4	10	88	4.4	26.4	> 270	281-283[20]
4*i*	4-OCH_3-C_6H_4	6	82	4.1	41	268-270	270-272[20]
4*j*	4-CH_3-C_6H_4	5	81	4.05	48.6	> 270	304-305[20]

[a]: Yields refer to isolated pure products.

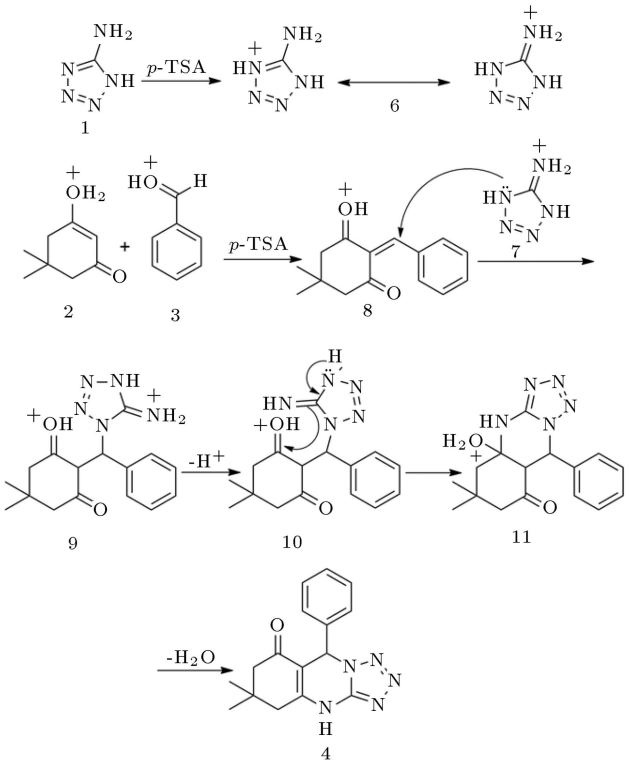
[b]: Turn Over Number (TON) is the ratio of the number of moles of the product to the number of moles of the catalyst.

[c]: Turn Over Frequency (TOF) is the number of molecules of a given product made per catalytic site per unit time.

Table 2. Synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline (4*c*) using different reagents and reaction conditions.

Entry	Reagent	Conditions	Time	Yield (%)[ref]
1	NaN_3 (2 mmol), $Hg(OAc)_2$ (1 mmol)	HOAc, 100°C	6 h	67[20]
2	I_2 (10 mol%)	*i*-PrOH, reflux	25 min	70[19]
3	*p*-TSA (20 mol%)	solvent-free, 80°C	9 min	90[a]

[a]: Referred to the present work.



Scheme 3. The plausible mechanism for the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline.

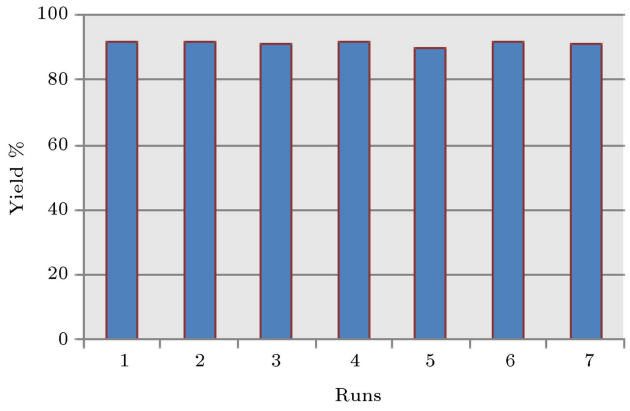


Figure 1. Recycling experiment of catalyst.

derivatives. The reaction mixture was washed with water (10 mL) after completion. The soluble catalyst was separated from the solid product and recovered after the evaporation of water. Then, the recycled catalyst was tested for its activity in subsequent runs (Figure 1).

It was very beneficial that *p*-TSA could be reused in seven cycles without any loss in its catalytic activity. Thus, the new procedure is environmentally friendly, cost effective, clean and more efficient than reported methods. This claim is justified through representative examples from more recently published literature, illustrated in Table 2.

4. Conclusion

In summary, the described, three component synthesis under solvent-free conditions is a simple, practical, environmentally friendly and very regioselective method for the preparation of some novel heterocyclic compounds containing tetrahydrotetrazolo[1,5-*a*]quinazoline, with the advantages of easy work-up and mild reaction conditions. The biological properties of the new compounds obtained in this research are under investigation.

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Biographies

Asadollah Hassankhani was born in Hashtrood, Iran, in 1976. He obtained his PhD degree in Organic Chemistry from the University of Sistan and Baluchestan, Iran, in 2008, and is currently Assistant Professor of Organic Chemistry at the Graduate University of Advanced Technology, Iran. His main research interests include catalysis, multi-component reactions, heterocycle synthesis and methodology.

Elaheh Mosaddegh was born in Kerman, Iran, in 1981. She obtained her PhD degree in Organic Chemistry from Shahid Bahonar University of Kerman, Iran, in 2009, and is currently Assistant Professor of Organic Chemistry at the Graduate University of Advanced Technology, Iran. Her main research interests include multi-component reactions, synthetic methodology, green chemistry, catalysis and nanoparticles.