Novel 1,2,3,4-Tetrahydroquinazolinones *via* Reaction of 2-Amino-*N*-substituted Benzamides and Dimethyl Acetylenedicarboxylate

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Reaction of 2-amino-*N*-substituted benzamides and dimethyl acetylenedicarboxylate (DMAD) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in H_2O at room temperature led to the formation of novel 1,2,3,4-tetrahydroquinazolinones.

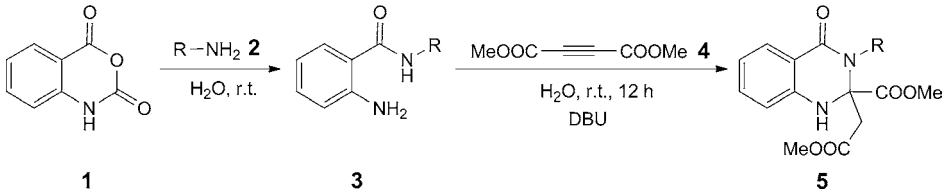
Introduction. – Over the last few decades, environment-friendly organic procedures have attracted lots of attention and among them, H_2O has been in the focus as an eco-friendly and economical reaction medium [1]. It is believed that H_2O-insoluble organic compounds undergo the desired reactions *via* hydrophobic interactions [2][3]. The efficiency of H_2O is not only associated with environment issues but also it has depicted special characteristics as compared to commonly employed organic solvents [4] leading to the development of in/on H_2O organic reactions.

Quinazoline derivatives are widespread structures existing in various natural products as well as bioactive compounds [5]. In this respect, 1,2,3,4-tetrahydroquinazolines possess a wide range of biological properties including antihypertensive [6], antioxidant [7], anti-inflammatory [8], antihepatitis [9], antimicrobial [10], antineurodegenerative [11], and anticancer [12] activities. Regarding the great significance of 1,2,3,4-tetrahydroquinazolines, developing efficient and user-friendly synthetic procedures for their preparation is desirable.

Considering few reports on the synthesis of the corresponding compounds [13–15]; herein, in continuation of our work on the synthesis of new heterocycles particularly bioactive quinazolinones [16–18], we report an efficient and unproblematic route for the synthesis of novel 1,2,3,4-tetrahydroquinazolinone derivatives through the reaction of 2-amino-*N*-substituted benzamides and dimethyl acetylenedicarboxylate (DMAD) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in H_2O at room temperature (*Scheme 1*).

Results and Discussion. – We initiated our investigations by the preparation of various 2-amino-*N*-substituted benzamides **3** through the reaction of isatoic anhydride

Scheme 1. *Synthesis of Quinazolinone Derivatives* **5**



(=2*H*-3,1-benzoxazine-2,4(1*H*)-dione; **1**) and amines **2** in H_2O at room temperature [17] (*Scheme 1*). Then, 2-amino-*N*-phenylbenzamide (**3a**) was reacted with DMAD (dimethyl but-2-ynedioate, **4**) under different conditions. Some results have been summarized in *Table 1*. Since solvents have an important influence on organic reactions, various organic solvents such as EtOH, MeCN, DMF, toluene, and CH_2Cl_2, as well as H_2O, were examined at room temperature. Our investigation revealed that protic solvents were more efficient, and the best yield was achieved using H_2O as a solvent. Thus, H_2O was vital in our reaction not only due to its environmental benefits, but also due to the other advantages. Also, it was found that a base is crucial to afford the related 1,2,3,4-tetrahydroquinazolinone **5a**, as no product at all was obtained in the absence of a base. Among various examined bases such as DBU, DABCO, Et_3N, NaOH, K_2CO_3, and $NaHCO_3$, DBU was found to be most effective (*Table 1*).

After the confirmation of the structure of product **5a** using IR, ^{1}H-, and ^{13}C-NMR spectroscopic methods, different reactions were conducted with various 2-amino-*N*-substituted benzamides **3** and DMAD (**4**) to build up different products **5** (*Table 2*).

A plausible mechanism for the formation of product **5** is depicted in *Scheme 2*. The reaction starts with the nucleophilic addition of the NH_2 group of the 2-amino-benzamide **3** to DMAD giving intermediate **6**, which is protonated by H_2O to form **7**.

Table 1. *Investigation of Various Conditions for the Formation of Product* **5a**

Entry	Solvent	Base	Yield [%][a])
1	H_2O	–	–
2	H_2O	DBU	70
3	H_2O	DABCO	45
4	H_2O	K_2CO_3	42
5	H_2O	Et_3N	40
6	H_2O	NaOH	32
7	H_2O	$NaHCO_3$	26
8	EtOH	DBU	45
9	EtOH	DABCO	30
10	DMF	DBU	42
11	MeCN	DBU	35
12	MeCN	DABCO	25
13	Toluene	DBU	25
14	CH_2Cl_2	DBU	10

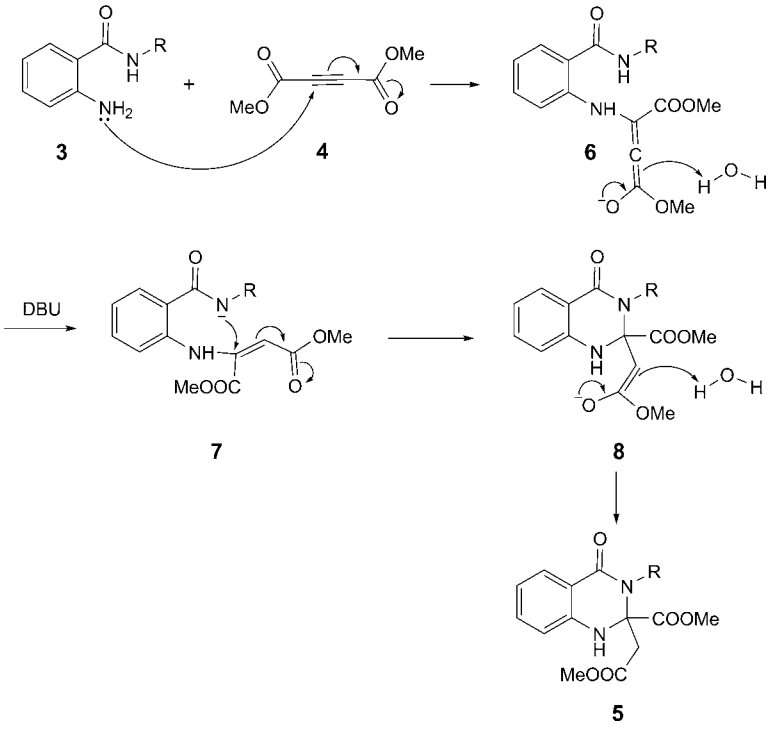
[a]) Yield of isolated product.

Table 2. *Synthesis of Quinazolinone Derivatives* **5**

Entry	R	Product	Yield [%][a])
1	Ph	**5a**	70
2	$PhCH_2$	**5b**	80
3	4-F–$C_6H_4CH_2$	**5c**	77
4	2-Cl–$C_6H_4CH_2$	**5d**	75
5	Furan-2-yl	**5e**	72
6	Cyclopentyl	**5f**	82
7	Cyclopropyl	**5g**	80
8	^{i}Pr	**5h**	85
9	Allyl	**5i**	80

[a]) Yield of isolated product.

Scheme 2. *Mechanism for the Synthesis of Quinazolinone Derivatives* **5**



In the presence of DBU, the amide NH is deprotonated to achieve the cyclization reaction affording **8**. Then, proton transfer leads to the formation of products **5**.

Conclusions. – In summary, we developed a practical, efficient, and user-friendly protocol for the synthesis of novel 1,2,3,4-tetrahydroquinazolinone derivatives *via* 2-amino-*N*-substituted benzamides and DMAD in the presence of 1,8-diazabicyclo-

[5.4.0]undec-7-ene (DBU) in H_2O at room temperature. Different benefits such as the eco-friendly procedure and the lack of time-consuming workup make this investigation useful for both organic and medicinal chemists to improve their drug discovery research based on 1,2,3,4-tetrahydroquinazolinones.

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Experimental Part

General. M.p.: *Kofler* hot-stage apparatus; uncorrected. IR Spectra: *Nicolet-Magna FTIR 550* spectrophotometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker FT-500* instrument; δ in ppm rel. to Me_4Si as internal standard. Elemental analyses: *VarioEL Elementar Analysensystem GmbH* CHNS; in %.

General Procedure for the Synthesis of 1,2,3,4-Tetrahydroquinazolinone Derivatives **5**. A mixture of 2-amino-*N*-substituted benzamide **3** (1 mmol), DMAD (**4**; 1 mmol), and DBU (1 mmol) in H_2O (8 ml) was stirred for 12 h at r.t. Upon completion of the reaction, the obtained precipitates were filtered off. The corresponding products **5** were purified by chromatography using petroleum ether/AcOEt (4 :1).

Methyl 1,2,3,4-Tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxo-3-phenylquinazoline-2-carboxylate (**5a**). White crystals. M.p. 155 – 157°. IR: 3278, 3120, 3007, 2950, 1745, 1641, 1617. ^{1}H-NMR: 2.95 (*d*, *J* = 16.0, CH_2, 1 H); 2.85 (*d*, *J* = 16.0, CH_2, 1 H); 3.65 (*s*, MeO); 3.70 (*s*, MeO); 6.00 (br. *s*, NH); 6.77 (*d*, *J* = 7.7, H–C(8)); 6.91 (*t*, *J* = 7.7, H–C(6)); 7.36 (*td*, *J* = 7.7, 1.5, H–C(7)); 7.40 – 7.47 (*m*, 5 arom. H); 7.94 (*dd*, *J* = 7.7, 1.5, H–C(5)). ^{13}C-NMR: 41.3; 52.2; 53.2; 76.1; 114.5; 119.8; 128.4; 128.7; 128.9; 129.5; 130.1; 134.0; 137.3; 144.7; 163.3; 170.4; 170.6. Anal. calc. for $C_{19}H_{18}N_2O_5$ (354.12): C 64.40, H 5.12, N 7.91; found: C 64.28, H 5.28, N 8.13.

Methyl 3-Benzyl-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5b**). White crystals. M.p. 137 – 138°. IR: 3287, 3120, 3065, 2950, 1735, 1638, 1614. ^{1}H-NMR: 2.91 (*d*, *J* = 16.2, CH_2, 1 H); 3.29 (*d*, *J* = 16.2, CH_2, 1 H); 4.69 (*d*, *J* = 16.5, CH_2, 1 H); 5.07 (*d*, *J* = 16.5, CH_2, 1 H); 3.63 (*s*, MeO; 3.70 (*s*, MeO); 6.02 (*s*, NH); 6.70 (*d*, *J* = 7.8, H–C(8)); 6.90 (*t*, *J* = 7.8, H–C(6)); 7.23 – 7.33 (*m*, 5 arom. H), 7.34 (*td*, *J* = 7.8, 1.5, H–C(7)), 7.947 (*dd*, *J* = 7.8, 1.5, H–C(5)). ^{13}C-NMR: 40.2; 45.5; 52.3; 53.1; 75.6; 114.4; 119.6; 126.9; 127.1; 128.5; 128.8; 130.0; 134.0; 137.8; 144.4; 163.4; 169.9; 170.9. Anal. calc. for $C_{20}H_{20}N_2O_5$ (368.14): C 65.21, H 5.47, N 7.60; found: C 65.43, H 5.31, N 7.76.

Methyl 3-(4-Fluorobenzyl)-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5c**). White crystals. M.p. 132 – 134°. IR: 3300, 3126, 3071, 2953, 1735, 1638, 1510. ^{1}H-NMR: 2.90 (*d*, *J* = 16.2, CH_2, 1 H); 3.28 (*d*, *J* = 16.2, CH_2, 1 H); 4.67 (*d*, *J* = 16.3, CH_2, 1 H); 4.99 (*d*, *J* = 16.3, CH_2, 1 H); 3.63 (*s*, MeO); 3.70 (*s*, MeO); 6.02 (br. *s*, NH); 6.70 (*d*, *J* = 8.0, H–C(8)); 6.90 (*t*, *J* = 8.0, 1.0, H–C(6)); 7.00 – 7.23 (*t*, *J* = 8.5, H–C(3′), H–C(5′)); 7.25 (*dd*, *J* = 8.5, 5.5, H–C(2′), H–C(6′)); 7.37 (*td*, *J* = 8.0, 1.3, H–C(7)); 7.95 (*dd*, *J* = 8.0, 1.4, H–C(5)). ^{13}C-NMR: 40.2; 44.7; 52.3; 53.2; 75.6; 114.3; 114.5; 115.3 (*d*, *J*(C,F) = 83.9); 119.7; 128.6 (*d*, *J*(C,F) = 8.0); 128.7; 133.6; 134.2; 144.4; 161.9 (*d*, *J*(C,F) = 244.1); 163.4; 169.8; 170.8. Anal. calc. for $C_{20}H_{19}FN_2O_5$ (386.13): C 62.17, H 4.96, N 7.25; found: C 62.32, H 5.18, N 7.38.

Methyl 3-(2-Chlorobenzyl)-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5d**). White crystals. M.p. 130 – 131°. IR: 3357, 3068, 2953, 2846, 1760, 1665, 1614. ^{1}H-NMR: 2.92 (*d*, *J* = 16.2, CH_2, 1 H); 3.28 (*d*, *J* = 16.2, CH_2, 1 H); 4.75 (*d*, *J* = 17.5, CH_2, 1 H); 5.17 (*d*, *J* = 17.5, CH_2, 1 H); 3.62 (*s*, MeO); 3.68 (*s*, MeO); 6.00 (br. *s*, NH); 6.74 (*d*, *J* = 7.8, H–C(8)); 6.91 (*t*, *J* = 7.8, H–C(6)); 7.20 – 7.71 (*m*, H–C(4′), H–C(6′)); 7.23 (*td*, *J* = 7.5, 1.9, H–C(5′)); 7.35 – 7.39 (*m*, H–C(7), H–C(3′)); 7.95 (*dd*, *J* = 7.8, 1.3, H–C(5)). ^{13}C NMR: 40.0; 43.3; 52.3; 53.3; 75.4; 114.4; 114.5; 119.7; 127.1; 127.8; 128.2; 128.7; 129.3; 131.9; 134.2; 134.9; 144.5; 163.5; 169.8; 170.6. Anal. calc. for $C_{20}H_{19}ClN_2O_5$ (402.10): C 59.63, H 4.75, N 6.95; found: C 59.48, H 4.61, N 7.14.

Methyl 3-(Furan-2-ylmethyl)-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5e**). White crystals. M.p. 115 – 117°. IR: 3306, 3123, 3014, 2956, 1757, 1735, 1644. ^{1}H-NMR: 3.12 (*d*, *J* = 16.1, CH_2, 1 H); 3.49 (*d*, *J* = 16.1, CH_2, 1 H); 4.67 (*d*, *J* = 16.3, CH_2, 1 H); 4.95 (*d*, *J* = 16.3, CH_2, 1 H); 3.62 (*s*, MeO); 3.69 (*s*, MeO); 6.00 (br. *s*, NH); 6.31 – 6.34 (*m*, 2 H of furan); 6.77 (*d*, *J* = 7.5,

H–C(8)); 6.86 (*t*, *J* = 7.5, H–C(6)); 7.30 – 7.34 (*m*, H–C(7), 1 H of furan); 7.91 (*dd*, *J* = 7.5, 1.3, H–C(5)). ^{13}C-NMR: 38.6; 40.5; 52.4; 53.3; 75.2; 108.7; 110.6; 114.3; 119.5; 127.1; 128.6; 134.0; 141.8; 144.2; 150.8; 163.0; 168.5; 170.1. Anal. calc. for $C_{18}H_{18}N_2O_6$ (358.12): C 60.33, H 5.06, N 7.82; found: C 60.50, H 4.84, N 7.69.

Methyl 3-Cyclopentyl-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5f**). White crystals. M.p. 93 – 95°. IR: 3266, 3120, 3017, 2950, 1745, 1635, 1489. ^{1}H-NMR: 1.48 – 1.56 (*m*, CH_2); 1.67 – 1.80 (*m*, CH_2); 2.00 – 2.02 (*m*, CH_2); 2.27 – 2.34 (*m*, CH_2); 3.27 (*d*, *J* = 16.1, CH_2, 1 H); 3.27 (*d*, *J* = 16.1, CH_2, 1 H); 3.40 (*quint.*, *J* = 8.0, NCH); 3.76 (*s*, MeO; 3.84 (*s*, MeO); 5.99 (br. *s*, NH); 6.64 (*d*, *J* = 7.9, H–C(8)), 6.84 (*t*, *J* = 7.9, H–C(6)); 7.30 (*td*, *J* = 7.9, 1.4, H–C(7)); 7.83 (*dd*, *J* = 7.9, 1.4, H–C(5)). ^{13}C NMR: 23.8; 24.2; 29.0; 29.9; 40.1; 52.2; 53.5; 59.3; 78.0; 114.0; 119.5; 127.8; 132.6; 133.6; 143.5; 161.3; 170.2; 171.3. Anal. calc. for $C_{18}H_{22}N_2O_5$ (346.15): C 62.42, H 6.40, N 8.09; found: C 62.28, H 6.53, N 7.90.

Methyl 3-Cyclopropyl-1,2,3,4-tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxoquinazoline-2-carboxylate (**5g**). White crystals. M.p. 97 – 99°. IR: 3294, 3141, 3056, 2950, 2864, 1735, 1623, 1489. ^{1}H-NMR: 0.76 – 0.79 (*m*, CH_2, 1 H); 0.82 – 0.87 (*m*, CH_2, 1 H); 0.89 – 0.95 (*m*, CH_2, 1 H); 1.00 – 1.06 (*m*, CH_2, 1 H); 2.48 – 2.51 (*m*, NCH); 3.70 (*d*, *J* = 16.0, CH_2, 1 H); 3.55 (*d*, *J* = 16.0, CH_2, 1 H); 3.70 (*s*, MeO); 3.76 (*s*, MeO); 6.70 (*d*, *J* = 7.9, H–C(8)); 6.84 (*td*, *J* = 7.8, 1.0, H–C(6)); 7.33 (*td*, *J* = 7.8, 1.5, H–C(7)); 7.90 (*dd*, *J* = 7.8, 1.5, H–C(5)). Anal. calc. for $C_{16}H_{18}N_2O_5$ (318.12): C 60.37, H 5.70, N 8.80; found: C, 60.15, H 5.91, N 8.66.

Methyl 1,2,3,4-Tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxo-3-(propan-2-yl)quinazoline-2-carboxylate (**5h**). White crystals. M.p. 87 – 89°. IR: 3284, 3135, 3044, 2953, 1742, 1635, 1538. ^{1}H-NMR: (*d*, *J* = 6.7, Me); 1.56 (*d*, *J* = 6.7, Me); 3.00 (*d*, *J* = 16.3, CH_2, 1 H); 3.31 – 3.34 (*m*, NCH, CH_2, 2 H); 3.75 (*s*, MeO); 3.84 (*s*, MeO); 5.80 (br. *s*, NH); 6.63 (*d*, *J* = 7.9, H–C(8)); 6.84 (*td*, *J* = 7.9, 1.0, H–C(6)); 7.30 (*td*, *J* = 7.9, 1.0, H–C(7)); 7.83 (*dd*, *J* = 7.9, 1.0, H–C(5)). ^{13}C-NMR: 19.8; 21.0; 40.0; 50.6; 52.2; 53.4; 77.7; 114.0; 115.4; 119.5; 127.9; 133.6; 143.6; 161.8; 170.3; 171.4. Anal. calc. for $C_{16}H_{20}N_2O_5$ (320.14): C 59.99, H 6.29, N 8.74; found: C 60.14, H 6.41, N 8.51.

Methyl 1,2,3,4-Tetrahydro-2-(2-methoxy-2-oxoethyl)-4-oxo-3-(prop-2-en-1-yl)quinazoline-2-carboxylate (**5i**). White crystals. M.p. 122 – 124°. IR: 3260, 3120, 3074, 3007, 2947, 1754, 1635. ^{1}H-NMR: (*d*, *J* = 16.3, CH_2, 1 H); 3.35 (*d*, *J* = 16.3, CH_2, 1 H); 3.74 (*s*, MeO; 3.84 (*s*, MeO); 4.05 (*ddt*, *J* = 16.7, 5.1, 1.6, NCH_2, 1 H); 4.37 (*ddt*, *J* = 16.7, 5.1, 1.6, NCH_2, 1 H); 5.16 (*dd*, *J* = 10.3, 1.4, =CH_2, 1 H); 5.20 (*dd*, *J* = 17.2, 1.4, =CH_2, 1 H); 5.87 (*ddt*, *J* = 17.2, 10.3, 5.1, =CH, 1 H); 5.95 (br. *s*, NH); 6.68 (*d*, *J* = 8.0, H–C(8)); 6.85 (*td*, *J* = 8.0, 1.0, H–C(6)); 7.31 (*td*, *J* = 8.0, 1.5, H–C(7)); 7.89 (*dd*, *J* = 8.0, 1.5, H–C(5)). ^{13}C-NMR: 40.4; 44.8; 52.3; 53.2; 77.2; 114.2; 114.4; 116.4; 119.5; 128.5; 133.8; 133.9; 144.2; 162.4; 170.0; 170.9. Anal. calc. for $C_{16}H_{18}N_2O_5$ (318.12): C 60.37, H 5.70, N 8.80; found: C 60.51, H 5.58, N 8.67.

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