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PPh_3-mediated reactions of diazoimides in water: a facile synthesis of fused triazine derivatives

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ABSTRACT

Triphenylphosphine-mediated reactions of diazoimides in water were carried out under mild conditions to afford several triazine derivatives in high yields. We have demonstrated an environment friendly methodology to synthesize triazine derivatives.

Water can participate in various organic reactions, such as hydrolysis, hydration, hydrogen exchange, and free radical oxidation chemistry.[1] Unlike the previous decades, where the use of water as a solvent had been restricted only to hydrolysis reactions, chemists have started investigating the possibility of using water as a solvent for other organic reactions, sometimes with surprising and novel results.[2] The importance of this green chemistry protocol lies in the fact that organic solvents cannot be cheaper than water, and are associated with risks such as flammable, explosive, and carcinogenic.[3a] Organic solvents are major contributors of environment.[3b] The investigation of organic reactions in water may also contribute to understanding basic mechanism of biological systems. 1,2,4-Triazines are a family of heterocycles that represent an important class of pharmaceutically important scaffolds, and their biological properties have been well studied.[4a] Examples are 6-aza-2′-oxyisocytidine (**1**), 6-aza-5-methyl-2′-deoxyisocytidine (**2**),[4b] 6-azauridine-5′-monophosphate (6-AzaUMP)[4c,d] (**3**) (a strong inhibitor of enzyme orotidine 5′-monophosphate decarboxylase), and tirapazamine (**4**)[4e] (a bioreductive as well as a substitute to *cis*-platin in chemotherapy for cancer) (Fig. 1).

With the intention of carrying out an eco-friendly aqueous phase reaction, we planned to employ diazoimides for this purpose. In continuation of our ongoing research work[5] centered on the exploitation of α-diazocarbonyl compounds, we sought to report the triphenylphosphine-mediated reactions of diazoimides in water to synthesize triazines. Toward this, we have chosen cyclic diazoimide **5a** and an equimolar amount of triphenylphosphine as the reactants in an aqueous medium, and allowed them to react at room temperature. The reactants were initially insoluble in water, gradually dissolved in the aqueous phase as the reaction proceeded, and became homogenous at the end of the reaction. The progress of the reaction was monitored by TLC, which showed the gradual disappearance of the starting materials. The aqueous phase was extracted using dichloromethane and concentrated.

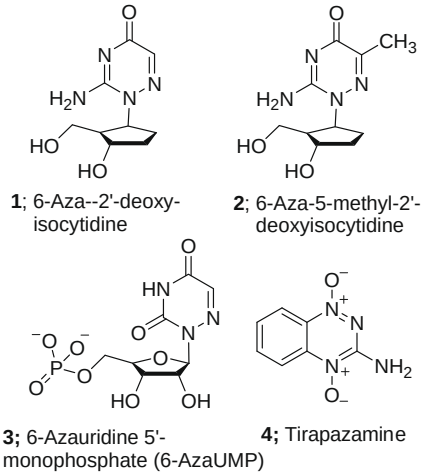

Figure 1. Biologically important triazine derivatives.

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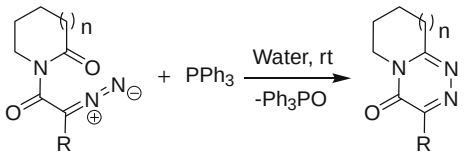
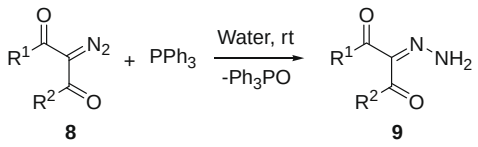


Scheme 1. Reaction of diazomides with triphenylphosphine.



Scheme 2. Reaction of diazocarbonyl compounds with PPh_3.

The residue was purified by column chromatography to furnish the interesting triazine derivative[6] **6a** in 85% yield (Scheme 1, Table 1, entry a) and triphenylphosphine oxide as the byproduct.

The structure of the product was confirmed by the characteristic disappearance of a carbonyl group and by the appearance of two imine quaternary carbons at $\delta = 150.8$, 149.2 in the ^{13}C NMR spectrum. The disappearance of the diazo group was also observed in the IR spectrum. With this encouraging result in the aqueous medium, we next explored the scope of the ring size and substituent in cyclic diazoimides. We also performed similar reactions on a series of cyclic diazoimides **5b–h** affording the corresponding triazine derivatives **6b–h** in excellent yields (Scheme 1, Table 1). In all the above-mentioned reactions, product **6** has the closer R_f value in TLC to triphenylphosphine oxide, which was formed as the byproduct. Care must be taken during the chromatographic isolation of the product. In order to analyze the feasibility of these reactions in organic solvents, we have chosen anhydrous dichloromethane, diethyl ether, and methyl alcohol (Table 1). Thus, these reactions were repeated in organic solvents to yield the corresponding triazine derivatives **6** in comparatively lower yields. In the above-mentioned experiments, we found that water is the most efficient solvent for these reactions. The reaction time is comparatively longer since the reactants are less soluble in water.

As an attempt to obtain a single crystal for a triazine, the products **6a** and **6c** were allowed to react with 2,4-dinitrophenylhydrazine to yield the corresponding yellow hydrazone derivatives **7a** and **7b** in very good yields. The carbonyl group of **6** is involved in the formation of the above-mentioned hydrazone derivatives. In order to understand the mechanism for the formation of triazines **6** in an aqueous medium, we planned to perform similar reactions on acyclic diazocarbonyl compounds. Thus, the treatment of a representative diazo ketone **8a** with PPh_3 in water afforded the corresponding hydrazones **9a** in good yields (Scheme 2, Table 2, entry a). This reaction was generalized with other diazo ketones **8b–g** and diazo esters **8h–k** to furnish the corresponding hydrazones **9b–k** (Scheme 2, Table 2). A related report[7] revealed that the treatment of the diazocarbonyl compound with triphenylphosphine in isopropyl ether and followed by water hydrolysis provided the corresponding hydrazone derivatives. In order to ana-

Table 2
Synthesis of hydrazones **9**

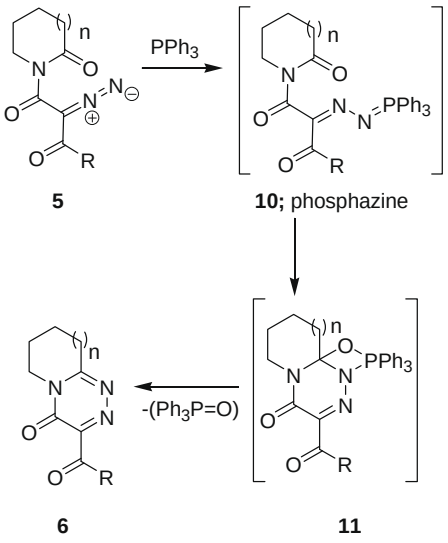
Entry	R^1	R^2	Time (min)	Yield[a] (%) of 9
a	*m*-Cl–C_6H_4-	H	60	85
b	CH_3–$(CH_2)_{14}$-	H	65	93
c	2-Thienyl-	H	50	95
d	Cyclohexyl-	H	50	95
e	*o*-CH_3-C_6H_4–	H	40	89
f	*m*-CH_3-C_6H_4-	H	20	93
g	Me	Me	80	90
h	Me	OEt	45	90
i	Cyclohexyl-O-	OEt	50	92
j	OMe	OMe	60	95
k	OEt	OEt	70	94

[a] Yields (unoptimized) refer to isolated pure compounds **9**.

Table 1
Synthesis of triazine derivatives **6** in different solvents

Entry	*n*	R	Product	Solvent	Time (min)	Yield[a] (%) of **6**
a	0	COMe	**6a**	H_2O	90	85
			6a	CH_2Cl_2	30	77
			6a	Et_2O	45	70
			6a	MeOH	35	85
b	1	COMe	**6b**	H_2O	120	85
			6b	CH_2Cl_2	40	75
			6b	Et_2O	50	72
			6b	MeOH	40	80
c	2	COMe	**6c**	H_2O	120	85
			6c	CH_2Cl_2	40	74
			6c	Et_2O	48	63
d	0	COOEt	**6d**	H_2O	90	95
			6d	CH_2Cl_2	45	85
			6d	Et_2O	50	87
			6d	MeOH	45	85
e	1	COOEt	**6e**	H_2O	120	95
			6e	CH_2Cl_2	55	90
f	2	COOEt	**6f**	H_2O	2.0	95
			6f	CH_2Cl_2	50	85
g	0	COOMe	**6g**	H_2O	60	90
			6g	CH_2Cl_2	40	80
h	2	COOMe	**6h**	H_2O	55	92
			6h	CH_2Cl_2	48	86

[a] Yields (unoptimized) refer to isolated pure compounds **6**.



Scheme 3. Proposed mechanism for the formation of triazine derivatives.

lyze the possibility of the formation of triazine **6** via the condensation of hydrazine with the amide carbonyl, the hydrazones **9g,h,j** were allowed to react with piperidin-2-one and 2-pyrrolidone in water as well as dichloromethane. These reactions did not furnish any condensed imine product, and the starting materials were recovered.

The above-mentioned PPh_3-mediated reactions proceeded with water and also with other anhydrous organic solvents. The mechanism can be proposed for the formation of triazine derivatives through the initial formation of the phosphazine[8] **10**, which subsequently combines with the ring carbonyl group to furnish the intermediate **11** (Scheme 3). The elimination of triphenylphosphine oxide would yield triazine **6**. Generally, the reaction of azides with PPh_3 afforded imines via the aza-Wittig reaction.[9] In the above-mentioned reaction, the diazo functional group remains intact in the presence of PPh_3 without nitrogen extrusion. As the above-mentioned reactions were performed under mild conditions, we did not observe the probable O–H insertion[10] with water or ketene formation[11] or decomposition.

In summary, we have demonstrated highly efficient PPh_3-mediated reactions of several diazoimides in water to afford the corresponding fused bicyclic triazine derivatives. This protocol is an easy and green procedure and could be an efficient methodology for the synthesis of other heterocycles. Moreover, the facile environmentally benign nature is the advantage of this method. The scope of this chemistry to synthesize various heterocycles using different trialkylphosphines is currently under progress in our laboratory.

Acknowledgments

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6. All new compounds gave satisfactory spectral data consistent with their structures and selected spectral data are given below. *General procedure for the synthesis of triazine derivatives.* (**6**): *3-Acetyl-7,8-dihydropyrrolo[2,1-c][1,2,4]-triazin-4(6H)-one* (**6a**): A 50 mL round bottomed flask was charged with the diazoimide **5a** (360 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water, and the reaction mixture was stirred well. The progress of the reaction mixture was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with dichloromethane. The solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography using silica gel (ethyl acetate/hexane 95:5, $R_f = 0.6$) to furnish 304 mg of 3-acetyl-7,8-dihydropyrrolo[2,1-*c*][1,2,4]triazin-4(6*H*)-one **(6a)** in 85% yield as a yellow thick oil. IR (film) 3521, 3440, 3058, 2985, 1727, 1680, 1568, 1471, 1413, 1364, 1281, 1162, 1040, 927, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.20 (2H, t, $J = 7.2$ Hz), 3.36 (2H, t, $J = 8.0$ Hz), 2.63 (3H, s, CH_3), 2.40–2.32 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 195.6 (C=O), 163.2 (C=O), 150.8 (*quat*-C), 149.2 (*quat*-C), 47.5 (CH_2), 31.3 (CH_2), 27.8 (CH_3), 18.3 (CH_2). HRMS (ESI) calcd for $C_8H_9N_3O_2$ $(M+Na)^+$ 202.0592, found 202.0625.
3-Acetyl-6,7,8,9-tetrahydropyrido[2,1-c][1,2,4]triazin-4-one **(6b)**: A 50 mL round bottomed flask was charged with the diazoimide **5b** (385 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water as described in the general procedure (ethyl acetate/hexane 90:10, $R_f = 0.6$) to furnish 345 mg of 3-acetyl-6,7,8,9-tetrahydropyrido[2,1-*c*][1,2,4]triazin-4-one **(6b)** in 85% yield as a yellow thick oil. IR (film) 3659, 3435, 3346, 3056, 2987, 2308, 1723, 1683, 1566, 1474, 1364, 1267, 1161, 1037, 965, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.23 (2H, t, $J = 7.3$ Hz), 3.35 (2H, t, $J = 8.0$ Hz), 2.64 (3H, s, CH_3), 2.43–2.22 (4H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 195.7 (C=O), 163.0 (C=O), 151.1 (*quat*-C), 149.3 (*quat*-C), 42.6 (CH_2), 32.4 (CH_2), 27.6 (CH_3), 18.3 (CH_2), 17.9 (CH_2). HRMS (ESI) calcd for $C_9H_{11}N_3O_2$ $(M+Na)^+$ 216.0749, found 216.0778.*3-Acetyl-7,8,9,10-tetrahydro[1,2,4]triazino[4,3-a]azepin-4(6H)-one* **(6c)**: A 50 mL round bottomed flask was charged with the diazoimide **5c** (410 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water as described in the general procedure (ethyl acetate/hexane 90:10, $R_f = 0.6$) to furnish 386 mg of 3-acetyl-7,8,9,10-tetrahydro[1,2,4]triazino[4,3-*a*]azepin-4(6*H*)-one **(6c)** in 95% yield as a yellow thick oil. IR (film) 3668, 3432, 3018, 2982, 1720, 1679, 1567, 1470, 1402, 1261, 965, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.29 (2H, t, $J = 5.0$ Hz), 3.12 (2H, t, $J = 5.6$ Hz), 2.65 (3H, s, CH_3), 1.87–1.78 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 195.7 (C=O), 163.1 (C=O), 151.3 (*quat*-C), 149.5 (*quat*-C), 42.7 (CH_2), 34.6 (CH_2), 29.1 (CH_2), 27.7 (CH_3), 26.5 (CH_2), 24.2 (CH_2). HRMS (ESI) calcd for $C_{10}H_{13}N_3O_2$ $(M+Na)^+$ 230.0905, found 230.0875.*Ethyl 4-oxo-4,6,7,8-tetrahydropyrrolo[2,1-c][1,2,4]triazine-3-carboxylate* **(6d)**: A 50 mL round bottomed flask was charged with diazoimide **5d** (450 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water as described in the general procedure (ethyl acetate/hexane 90:10, $R_f = 0.6$) to furnish 386 mg of ethyl 4-oxo-4,6,7,8-tetrahydropyrrolo[2,1-*c*][1,2,4]triazine-3-carboxylate **(6d)** in 80% yield as a yellow thick oil. IR (film) 3455, 2986, 1742, 1693, 1571, 1484, 1410, 1341, 1285, 1189, 1085, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.48–4.37 (2H,m), 4.20 (2H, t, $J = 7.4$ Hz), 3.32 (2H, t, $J = 7.8$ Hz), 2.40–2.25 (2H, m), 1.40 (3H, t, $J = 7.0$ Hz, CH_3); ^{13}C (50.3 MHz, $CDCl_3$) 162.5 (C=O), 161.7 (C=O), 149.3 (*quat*-C), 148.8 (*quat*-C), 62.0 (CH_2), 47.5 (CH_2), 31.1 (CH_2), 18.2 (CH_2), 13.7 (CH_3). HRMS (ESI) calcd for $C_9H_{11}N_3O_3$ $(M+Na)^+$ 232.0698, found 232.0689.
Ethyl 4-oxo-6,7,8,9-tetrahydro-4H-pyrido[2,1-c][1,2,4]triazine-3-carboxylate (**6e**): A 50 mL round bottomed flask was charged with the diazoimide **5e** (480 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water as described in the general procedure (ethyl acetate/hexane 90:10 $R_f = 0.6$) to furnish 357 mg of ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[2,1-*c*][1,2,4]triazine-3-carboxylate **(6e)** in 80% yield as a yellow thick oil. IR (film) 3462, 2991, 1739, 1682, 1565, 1476, 1328, 1260, 1188, 1078, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.50–4.40 (2H, m), 3.96 (2H, t, $J = 5.8$ Hz), 3.08 (2H, t, $J = 6.4$ Hz), 2.04–1.95 (4H,m), 1.41 (3H, t, $J = 7.2$ Hz, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) 162.2 (C=O), 158.1 (C=O), 150.4 (*quat*-C), 148.3 (*quat*-C), 62.2 (CH_2), 42.3 (CH_2), 28.7 (CH_2), 21.0 (CH_2), 18.0 (CH_2), 13.9 (CH_3). HRMS (ESI) calcd for $C_{11}H_{13}N_3O_3$ $(M+Na)^+$ 246.0855, found 246.0895.
Methyl 4-oxo-4,6,7,8-tetrahydropyrrolo[2,1-c][1,2,4]triazine-3-carboxylate **(6g)**: A 50 mL round bottomed flask was charged with the diazoimide **5a** (420 mg, 2 mmol) and PPh_3 (524 mg, 2.2 mmol) in water as described in the general procedure (ethyl acetate/hexane 90:10, $R_f = 0.6$) to furnish 312 mg of methyl 4-oxo-4,6,7,8-tetrahydropyrrolo[2,1-*c*][1,2,4]triazine-3-carboxylate **(6f)** in 80% yield as a yellow thick oil. IR (film) 3444, 2998, 1737, 1688, 1561, 1476, 1414, 1325, 1288, 1179, 1080, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.21 (2H, t, $J = 7.2$ Hz), 3.97 (3H, s, CH_3), 3.34 (2H, t, $J = 8.0$ Hz), 2.41–2.26 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 162.7 (C=O), 162.2 (C=O), 149.4 (*quat*-C), 148.6 (*quat*-C), 52.9 (CH_3), 47.7 (CH_2), 31.2 (CH_2), 18.4 (CH_2). HRMS (ESI) calcd for $C_8H_9N_3O_3$ $(M+Na)^+$ 218.0542, found 218.0527.
3-[(1E)-N-(2,4-Dinitrophenyl)ethane-hydrazonoyl]-7,8,9,10-tetrahydro[1,2,4]-

triazino[4,3-a]azepin-4(6H)-one (**7c**): 3-Acetyl-7,8,9,10-tetrahydro[1,2,4]-triazino[4,3-a]azepin-4(6*H*)-one (**6c**) (2 mmol) in methanol was stirred well to get a clear solution. To this mixture, 2,4-dinitrophenylhydrazine was added and stirred well for 1 h. The obtained yellow solid was filtered off to furnish 735 mg of 3-[(1*E*)-*N*-(2,4-dinitrophenyl)ethanehydrazonoyl]-7,8,9,10-tetrahydro-[1,2,4]triazino[4,3-*a*]azepin-4(6*H*)-one (**7c**) in 95% yield as a yellow solid; mp 136–137 °C. IR (KBr) 3362, 3313, 3179, 3106, 2922, 2855, 1682, 1614, 1590, 1533, 1506, 1461, 1330, 1310, 1270, 1138, 1059, 968, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 11.39 (1H, br s, NH), 9.16 (1H, d, J = 2.6 Hz), 8.31 (1H, dd, J_1 = 2.6 Hz, J_2 = 29.2 Hz), 8.22 (1H, d, J = 9.6 Hz), 4.35 (2H, t, J = 4.6 Hz), 3.14 (2H, t, J = 2.8 Hz), 2.53 (3H, s, CH_3), 1.91–1.72 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 160.8 (C=O), 151.9 (*quat*-C), 150.4 (*quat*-C), 148.3 (*quat*-C), 144.7 (*quat*-C), 139.2 (*quat*-C), 130.4 (*quat*-C), 130.2 (*Arom*-CH), 123.0 (*Arom*-CH), 117.7 (*Arom*-CH), 43.1 (CH_2), 34.8 (CH_2), 29.5 (CH_2), 27.0 (CH_3), 24.8 (CH_2), 12.7 (CH_2). HRMS (ESI) calcd for $C_{16}H_{17}N_7O_5$ $(M+Na)^+$ 410.1189, found 410.1167.

1-(3-Chlorophenyl)-hydrazonoethanone (**9a**): Diazo ketone **8a** (360 mg, 2 mmol) was treated with PPh_3 (524 mg, 2.2 mmol) as described in the general procedure to afford **9a** (ethyl acetate/hexane 55:45, R_f = 0.6) in 78% yield as a yellow solid; mp 105–107 °C. IR (KBr) 3362, 3179, 1586, 1557, 1482, 1089, 1006, 796, 563 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 9.87 (2H, s, NH_2), 7.99–7.85 (2H, m, arom-*H*), 7.56–7.27 (2H, m, arom-*H*), 5.61 (1H, s, C*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) 192.1 (C=O), 137.4 (*quat*-C), 131.2 (*quat*-C), 129.3 (CH), 129.0 (CH), 128.2 (CH), 123.1 (CH). HRMS (ESI) calcd for $C_8H_7ClN_2O$ $(M+Na)^+$ 205.0144, found 205.0112.

2-Hydrazonomalonic acid diethyl ester (**9b**): Diazo ketone **8a** (370 mg, 2 mmol) was treated with PPh_3 (524 mg, 2.2 mmol) as described in the general procedure to afford **9b** (ethyl acetate/hexane 55:45, R_f = 0.6) in 94% yield as a colorless solid; mp 110–111 °C. IR (KBr) 3328, 3187, 2991, 2939, 2906, 1690, 1671, 1581, 1499, 1369, 1336, 1253, 1194, 1017, 807, 785, 480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 9.79 (2H, s, NH_2), 4.37–4.25 (4H, m), 1.39–1.31 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) 163.2 (C=O), 162.4 (C=O), 120.5 (*quat*-C), 60.7 (CH_2), 60.6 (CH_2), 14.0 (CH_3), 13.8 (CH_3). HRMS (ESI) calcd for $C_7H_{12}N_2O_4$ $(M+Na)^+$ 211.0695, found 211.0673.

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