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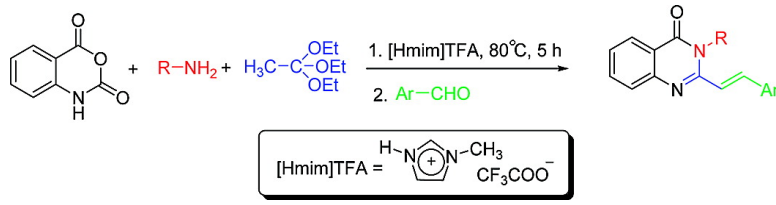

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Novel and Efficient One-Pot Tandem Synthesis of 2-Styryl-Substituted 4(3*H*)-Quinazolinones

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A novel one-pot tandem synthesis of 2-styryl-4(3*H*)-quinazolinones in an acidic ionic liquid is reported. In this procedure isatoic anhydride, a primary aniline or ammonium acetate, and triethylorthoacetate are reacted in the presence of imidazolium trifluoroacetate [Hmim]TFA. Subsequently an aromatic aldehyde is added to the mixture to afford the title compounds in high to excellent yields.

Multicomponent reactions (MCRs), an important subclass of tandem reactions, are one-pot processes in which three or more easily accessible components react to form a single product, which incorporates essentially all of the atoms of the starting materials.[1] MCRs are highly flexible, (chemo)selective, convergent, and atom-efficient processes of high exploratory power.[2] As such they closely approach the concept of ideal synthesis. Heterocyclic systems are common structural elements in many natural products and pharmacologically active substances. Accordingly, the development of efficient methods for the synthesis of (combinatorial libraries of) heterocyclic compounds has been posing a real challenge to organic chemists for over a century. In the course of time, MCRs have proved a convenient tool for the construction of many heterocyclic compound classes.[1,2]

The quinazolinones (**1**) (Figure 1) have been reported to possess a vast range of biological activities.[3] Among the various classes of 4(3*H*)-quinazolinones, 2-styryl substituted derivatives **2** form an important component of pharmacologically active compounds because they are associated with a wide spectrum of biological activities ranging from inhibitory effects on tubulin polymerization[4] to anticonvulsant **2u** (piriqualone).[5] Although there are many reports describing the synthesis of 4(3*H*)-quinazolinones,[6] most of these approaches are limited in that only phenyl groups at R^1 are tolerated.[6] There are only a few specific reports on the preparation of the 2-styryl-substituted 2,3-disubstituted quinazolin-4(3*H*) -ones.[5−9] The general method for the synthesis of these derivatives is the Knoevenagel condensation of 2-methyl-substituted quinazolinones **3** with aromatic aldehydes under basic[5,7] or acidic[8] conditions (Figure 2). However, this method suffers from certain drawbacks such as requiring multistep procedure, costly reagents, harsh reaction conditions, complex experimental processes, and low yields.[5,7,8]

Ionic liquids (ILs) have attracted an increasing interest in the context of green synthesis during recent years. Although ILs were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility,[10] today they have marched far beyond this border, showing their significant role in controlling the reaction as catalysts.[11]

As a continuation of our interest in the synthesis of quinazolinone rings,[12,13] here we report on a novel one-pot tandem synthesis of 2-styryl substituted 4(3*H*)-quinazolinones. We recently described an efficient, three-component, one-pot reaction for the synthesis of various 2,3-disubstituted 4(3*H*)-quinazolinones from readily available isatoic anhydride **4**, orthoesters **5**, and amines **6** in the presence of acidic catalyst (Figure 3).[13] This novel approach allows accessing a broader chemistry scope relative to the previously existing

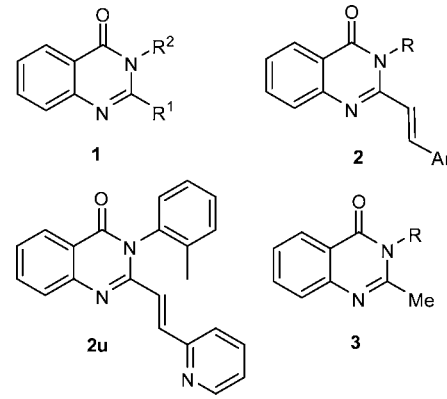

Figure 1. Structure of 4(3*H*)-quinazolinone and its derivatives.

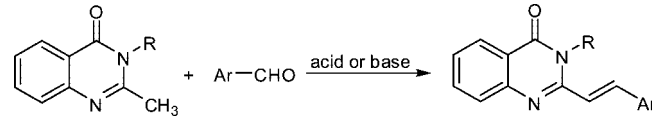

Figure 2. General method for the synthesis of 2-styryl quinazolinones.

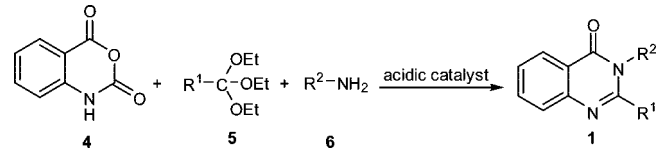

Figure 3. One-pot three-component synthesis of 4(3*H*)-quinazolinones.[13]

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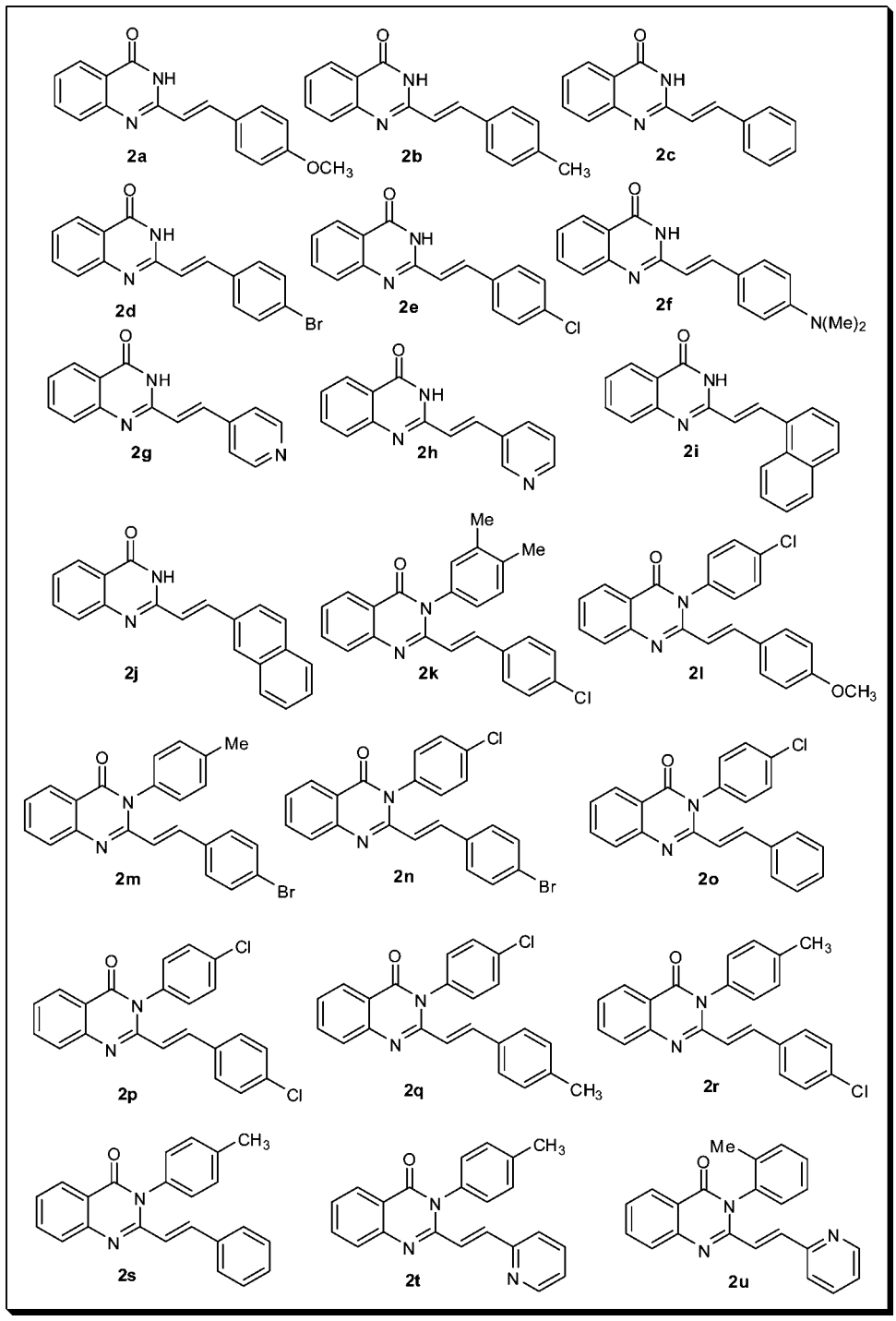

Figure 4. Library products **2a**−**2u** obtained by a four-component tandem reaction.

methods, accommodating an expanded array of orthoesters and amines. By this method, 2-methyl-substituted quinazolinones, which are the key intermediates in the synthesis of 2-styryl quinazolinones, are easily prepared.[13]

Results and Discussion

Recently, 1-methylimidazolium trifluoroacetate ([Hmim]-TFA)[14] has been used as an efficient acidic IL for the synthesis of heterocyclic compounds. It was also shown that [Hmim]TFA promotes the Knoevenagel condensation of CH-acid compounds and aromatic aldehydes.[15] So we decided to investigate the one-pot synthesis of 2-styryl-substituted 4(3*H*)-quinazolinones in the presence of [Hmim]TFA. After extensive optimization, we found that the two steps could be carried out in a general and efficient one-pot process to afford a variety of 2-styryl quinazolinones. As outlined in Scheme 1, the addition of 0.1 g of [Hmim]TFA to a reaction mixture composed of a 1:1:1 ratio of isatoic anhydride **4**/amine **6**/triethyl orthoacetate **7** at 80 °C for 5 h, was optimal for the formation of 2-methylquinazolinones. Subsequent treatment of the reaction mixture with 1 equiv of an aromatic aldehyde **8**, followed by heating at 80 °C for 4−7 h, afforded 2-styryl-substituted 4(3*H*)-quinazolinones (**2a**−**2u**) in yields typically exceeding 70% (Table 1).

Scheme 1. One-Pot Tandem Synthesis of 2-Styryl-Substituted 4(3*H*)-Quinazolinones

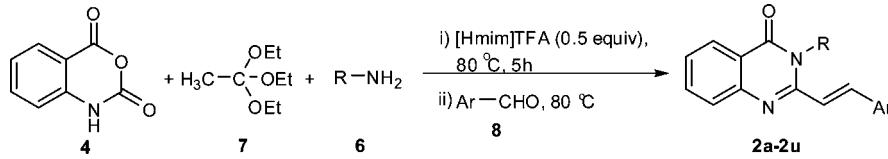

Table 1. Synthesis of 2-styryl-4(3*H*)-quinazolinones

product	R	Ar	yield (%)[a]	time (h)
2a	H	4-$CH_3OC_6H_4$	80	10
2b	H	4-$CH_3C_6H_4$	78	12
2c	H	C_6H_5	75	10
2d	H	4-BrC_6H_4	75	9
2e	H	4-ClC_6H_4	81	9
2f	H	4-$(CH_3)_2NC_6H_4$	82	10
2g	H	3-pyridyl	80	10
2h	H	4-pyridyl	79	11
2i	H	2-naphtyl	78	9
2j	H	1-naphtyl	80	9
2k	3,4-$(CH_3)_2C_6H_3$	4-ClC_6H_4	81	10
2l	4-ClC_6H_4	4-$CH_3OC_6H_4$	80	10
2m	4-$CH_3C_6H_4$	4-BrC_6H_4	78	9
2n	4-ClC_6H_4	4-BrC_6H_4	82	10
2o	4-ClC_6H_4	C_6H_5	78	10
2p	4-ClC_6H_4	4-ClC_6H_4	78	12
2q	4-ClC_6H_4	4-$CH_3C_6H_4$	80	12
2r	4-$CH_3C_6H_4$	C_6H_5	75	12
2s	4-$CH_3C_6H_4$	4-ClC_6H_4	80	12
2t	4-$CH_3C_6H_4$	2-pyridyl	70	12
2u	2-$CH_3C_6H_4$	2-pyridyl	71	12

[a] Yield based on isatoic anhydride.

Aromatic aldehydes carrying different functional groups work satisfactorily in the reaction (Table 1). Therefore, it can be concluded that no obvious effects from the electronic properties or nature of the aromatic ring substituents were observed in the above reactions. Prominent among the advantages of this new method are operational simplicity, good yields, and an easy workup procedure without using any chromatographic methods. One of the them is that a new member of styrylquinazolinones could be synthesized. Pyridylvinylquinazolinones (**2g** and **2h**), which have shown anticonvulsant, hypotonic, tranquilizing, and muscle relaxant activities,[7] were synthesized successfully in high yields (Figure 4).

In summary, this study offers a novel one-pot tandem procedure for the synthesis of 2-styryl-substituted 4(3*H*)-quinazolinones. To the best of our knowledge, this is the first report on the one-pot synthesis of 2-styryl quinazolinones. In this procedure, one C=C bond and four C−N bonds are formed in a tandem one-pot process that could be compared with other important reactions in multicomponent chemistry.[1,2] Furthermore, the workup procedure is very simple without using any chromatographic method. Starting materials are inexpensive and commercially available. By using different types of amines and aromatic aldehydes, we could obtain novel libraries of quinazolinones that make the method suitable for combinatorial and parallel synthesis in drug discovery.

Experimental Section

General Procedure for the One-Pot Synthesis of 2-Styryl-4(3*H*)-Quinazolinones. To a mixture of isatoic anhydride (1 mmol), a primary amine or ammonium acetate (1 mmol), and triethylorthoacetate (1 mmol) was added 0.1 g of [Hmim]TFA, and the mixture was heated at 80 °C. After 5 h, aromatic aldehyde (1 mmol) was added to the mixture, and it stirred for the appropriate time (see Table 1). After completion of the reaction, which was indicated by TLC (eluent *n*-hexane/ethyl acetate 2/1), water was added to the mixture and filtered. The crude product was recrystallized from ethanol.

2-(4-Methoxystyryl) Quinazolin-4(3*H*)-one (2a): mp 276−278 °C; IR (KBr) (ν_{max}, cm^{-1}) 3448, 1676, 1602; ^1H NMR (DMSO-d_6) δ_H 3.76 (3H, s, OCH_3), 6.82 (1H, d, J = 15 Hz, CH), 6.84−8.07 (9H, m, arom + CH), 12.23 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C 55.73, 114.96, 118.87, 121.41, 126.29, 127.44, 128.04, 129.72, 134.87, 138.48, 149.61, 152.17, 161.06, 162.24; MS (*m*/*z*, %) 278 (M^+, 75), 277 (100), 234 (30), 119 (25); Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278.31) C 73.37, H 5.07, N 10.07%; Found C 73.21, H 5.11, N 10.11%.

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Supporting Information Available. Experimental details and characterization data including IR, mass, ^1H, ^{13}C NMR, and CHN analysis for new compounds (**2a**−**2e** and **2k**−**2s**). This information is available free of charge via the Internet at http://pubs.acs.org.

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