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A novel approach for synthesis of 3-amino-5-aryl-2,5-dihydropyridazines using onium salt as soluble support

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Abstract

In this work it was presented an application of task specific onium salt as soluble support for the synthesis of 3-amino-5-aryl-2,5-dihydropyridazines. This soluble support is of wide applicability and combines advantages of solid phase synthesis without its limitations with those of solution phase chemistry. After a simple washing step, products were cleaved from the supports and obtained in good yields.

Keywords: Onium salt; Support; Synthesis; Pyridazines

Following the pioneering work done by Merrifield [1], great progress has been made in the solid-phase organic synthesis (SPOS). However, SPOS suffers a series of problems inherent to the heterogeneous nature of mixtures. Soluble polymer supports such as poly(ethylene glycols) [2] and non-cross-linked polystyrene [3] allow performing reactions in solution and have been demonstrated to be possible alternatives to solid supports. However, low loading capacity has narrowed their applicability. Hence the organic chemists have been seeking for a new, valuable soluble support for combinational chemistry and high-throughput parallel synthesis.

According to an exponentially growing literature, task specific onium salts have been considered as a new, valuable alternative to the soluble supports in supported organic synthesis [4]. Removing most disadvantages of solid phase and soluble polymer supported synthesis, it allows for high loading capacity, easy reaction monitoring and product characterization using TLC, NMR, HPLC, MS and IR, and keeps all the advantages of soluble supports and solid supports including easy purification by simple filtration and washes. More importantly, having a melting point over 100 °C, task specific onium salts made the purification simpler than traditional ionic liquids [5]. Having these advantages in mind, task specific onium salts supported synthesis has been applied to peptide synthesis [6], transition metal catalyzed reactions [7] and multicomponent reactions [8].

The chemistry of pyridazines and condensed pyridazines is now receiving considerable interest. These compounds show remarkable potency in various biological targets, including antithrombotic, antibiotic, and antitumor activity [9]. Many literatures reported the synthesis of this class of bioactive compounds in conventional liquid methods [10].

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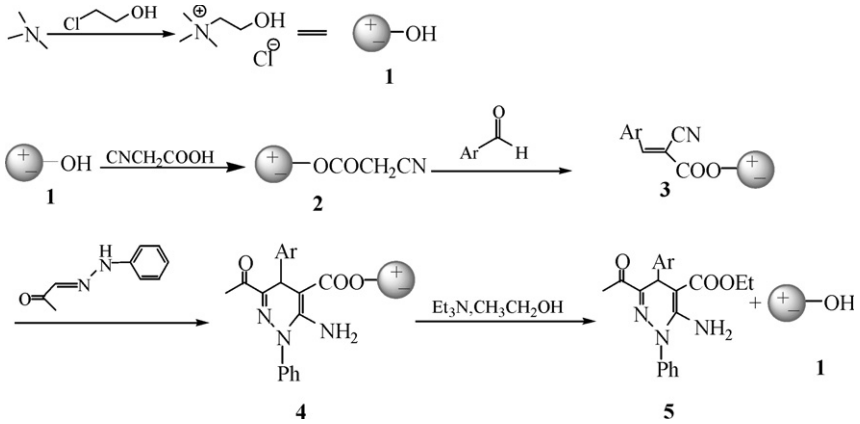

Scheme 1.

Taking the above facts into account, here we report a new approach for synthesis 3-amino-5-aryl-2,5-dihydropyridazines using onium salt as soluble support (Scheme 1). As shown in Scheme 1, trimethylamine was reacted with chloroethyl alcohol to give trimethyl-2-hydroxyethylammonium chloride (onium salt) **1** in 98% yield [11]. The onium salt **1** appears as a singlet in the 3.15 ppm since the trimethylammonium group of the support and furthermore with the chloride anion confers a good aqueous solubility. Using the hydroxy group as a linker, onium salt supported cyanoacetate **2** was synthesized by treatment of **1** with cyanoacetic acid in the presence of *N*,*N*′-dicyclohexylcorbodimide and catalytic amount of 4-(dimethylamino) pyridine in dry CH_3CN under N_2 [12]. The disappearance of the hydroxy group at 3323 cm^{-1} and appearance of the ester carbonyl and cyano group at 1752 cm^{-1} and 2217 cm^{-1} in IR spectrum were clear evidences for the formation of **2**. Compound **2** was reacted with a series of aromatic aldehydes to afford **3** through Knoevengel condensation [13]. In this step Knoevengel condensation could be easily carried out at room temperature in 95% ethanol without any other catalyst. This is because of the catalytic activity of ionic liquid in Knoevengel condensation [14]. So in this step, the onium salt played not only as a support but also as a catalyst. Onium salt supported cinnamonitriles **3** were then treated with 1-phenylhydrazo-nopyruvaldehydes in the presence of piperdine to obtain onium salt supported 3-amino-2-phenyl-5-aryl-6-acetyl-2,5-dihydropyridazines **4** through Michael addition [15]. The completion of Michael addition reaction was evidenced by the disappearance of cyano group at 2217 cm^{-1} and the appearance of amino group at 3326 cm^{-1} in IR spectrum. Concerning cleavage from the support, simple treatment by Et_3N in methanol afforded 3-amino-2-phenyl-5-aryl-6-acetyl-2,5-dihydropyridazines **5** [16]. The crude products were purified by flash chromatography to afford **5** in good yields.

To study the generality of this method, the reactions of onium salt supported cyanoacetate **2** with a variety of aromatic aldehydes were investigated. The presence of electron donating or electron withdrawing group on the aromatic ring of aldehydes, irrespective of their positions in the ring did not make any obvious difference in terms of the yields of pyridazines. They gave the expected results with good yields for almost all the tested substrates. Except **5a**, the other nine products have never been reported, and the results are summarized in Table 1. The end-products were characterized by ^1H NMR, ^{13}C NMR, HRMS and IR [17]. In all cases, the onium salt supported intermediates and products were purified by filtration followed by washing with Et_2O, which eliminates unreacted reagents and eventual non-supported side products. This procedure simplifies to a large extent previously reported methodologies in

Table 1
Synthesis of 3-amino-5-aryl-2,5-dihydropyridazines using onium salts as support.

Entry	Product	Ar	Yield[a]	Entry	Product	Ar	Yield[a]
1	**5a**	C_6H_5	80%	6	**5f**	2,4-$Cl_2C_6H_3$	81%
2	**5b**	2-$NO_2C_6H_4$	78%	7	**5g**	4-BrC_6H_4	82%
3	**5c**	3-$NO_2C_6H_4$	77%	8	**5h**	4-CNC_6H_4	77%
4	**5d**	4-$NO_2C_6H_4$	75%	9	**5i**	4-$CH_3OC_6H_4$	82%
5	**5e**	4-ClC_6H_4	82%	10	**5j**	4-OHC_6H_4	80%

[a] Isolated overall yield.

homogeneous phase as no complicated purification was needed. Moreover, the onium salt could be recycled in 95% yield and reused more than three times without appreciable decrease in yield and reaction activity.

In summary, we have developed a novel approach for the parallel synthesis of 3-amino-5-aryl-2,5-dihydropyridazines in good yields, and nine products have never been reported. The use of this novel onium salt support offers many advantages compared to previously reported supports including environmental friendliness, much higher loading capacity, easy isolation and purification of the products, higher yields, no need for use of large excess of reagents, standard analytical methods (IR, NMR, TLC) to monitor reaction progress, and recycling of the soluble support.

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[11] Synthesis of trimethyl-2-hydroxyethylammonium chloride **1**: To a solution of chloroethyl alcohol (5.8 mL, 79.1 mmol) in CH_3CN (15 mL) was successively added trimethylamine solution (33%) in methanol (15.0 mL). After vigorous stirring at 70 °C under N_2 for 14 h, solvents were removed under vacuum. Upon addition of Et_2O, the residue crystallized. Crystals were filtered off and washed with Et_2O to afford white solid **1** (9.6 g, 98%) in pure form.
[12] Synthesis of onium salt supported cyanoacetate **2**: Cyanoacetic acid (3.1 g, 37.2 mmol), DCC (12.4 g, 60.7 mmol), DMAP (0.9 g, 8.1 mmol) were added to a solution of **1** (5.5 g, 40.5 mmol) in dry CH_3CN (50 mL). The mixture was stirred at 25 °C under N_2 for 8 h. The insoluble *N*,*N*′-dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and washed with Et_2O, and then dried under vacuum to give **2** (7.8 g, 94%) as yellow oil.
[13] General preparation of onium salt supported cinnamonitriles **3**: To a solution of **2** (4.0 g, 19.3 mmol) in 95% EtOH (10 mL) was added the appropriate aromatic aldehyde (16 mmol). The solution was stirred at r.t. for 12 h and removed the solvent under reduced pressure. Upon addition of Et_2O, the residue crystallized. Crystals were filtered off and washed with Et_2O to afford product **3** in pure form.
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[15] Synthesis of onium salt supported 3-amino-2-phenyl-5-aryl-6-acetyl-2,5-dihydropyridazines **4**: To a stirred solution of **3** (5 mmol) in 95% EtOH (10 mL) was added 1-phenylhydrazonopyruvaldehydes (6 mmol) and catalytic amount piperdine (0.1 mmol). The mixture were stirred at 70 °C for 8 h, and then concentrated under reduced pressure. Upon addition of Et_2O, the residue crystallized. Crystals were filtered off and washed with Et_2O to afford product **4** in pure form.
[16] Synthesis of 3-amino-2-phenyl-5-aryl-6-acetyl-2,5-dihydropyridazines **5**: To a solution of **4** (3 mmol) in dry EtOH (15 mL) was added Et_3N (1.0 mL, 1.23 mmol). After stirring at 70 °C for 18 h, the solvent was removed under reduced pressure. The residue was washed with Et_2O.

Combined organic fractions were concentrated under vacuum and subsequently purified by flash chromatography on silica gel (EtOAc:*n*-hexane, 1:10) to give the products **5a–j**.

[17] The data of new compounds: **5b**: mp: 141–142 °C. IR (NaCl): 3420, 3321, 1664, 1612 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 6.6 Hz, CH_3), 2.38 (s, 3H, CH_3-CO), 4.12 (m, 2H, CH_2), 5.33 (s, 1H, CH pyridazine), 6.21 (s, 2H, NH_2), 7.22–7.84 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.88, 33.95, 59.66, 76.52, 125.73, 126.11, 126.83, 127.29, 127.65, 127.91, 129.03, 132.44, 139.66, 141.58, 147.37, 148,21, 150.31, 152.79, 168.95, 196.60; HRMS calcd. for $C_{21}H_{20}N_4O_5[M^+]$ 408.1434, found 408.1440. **5c**: mp: 151–152 °C. IR (NaCl): 3429, 3322, 1668, 1614 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 2.39 (s, 3H, CH_3-CO), 4.13 (m, 2H, CH_2), 5.41 (s, 1H, CH pyridazine), 6.28 (s, 2H, NH_2), 7.26–7.66 (m, 7H, ArH), 8.01 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.45, 24.86, 33.94, 59.68, 76.51, 125.77, 126.22, 126.83, 127.39, 127.61, 127.92, 129.03, 132.44, 139.66, 141.58, 147.39, 148.11, 150.31, 152.79, 168.90, 196.61; HRMS calcd. for $C_{21}H_{20}N_4O_5[M^+]$ 408.1434, found 408.1437. **5d**: mp: 174–175 °C. IR (NaCl): 3430, 3321, 1664, 1610 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 6.6 Hz, CH_3), 2.39 (s, 3H, CH_3-CO), 4.11 (m, 2H, CH_2), 5.44 (s, 1H pyridazine), 6.25 (s, 2H, NH_2), 7.26–7.56 (m, 7H, ArH), 8.13 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.84, 33.95, 59.61, 75.92, 125.73, 126.11, 126.83, 127.29, 127.64, 127.93, 129.02, 132.41, 139.62, 141.58, 141.91, 147.38, 150.30, 152.77, 168.88, 196.61; HRMS calcd for $C_{21}H_{20}N_4O_5[M^+]$ 408.1434, found 408.1436. **5e**: mp: 171–172 °C. IR (NaCl): 3433, 3327, 1663, 1611 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 6.6 Hz, CH_3), 2.38 (s, 3H, CH_3-CO), 4.12 (m, 2H, CH_2), 5.32 (s, 1H pyridazine), 6.24 (s, 2H, NH_2), 7.22–7.55 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.44, 24.83, 33.96, 59.62, 75.91, 125.75, 126.12, 126.86, 127.30, 127.62, 127.91, 129.02, 132.41, 139.62, 141.58, 141.91, 147.38, 150.30, 152.77, 168.81, 196.60; HRMS calcd. for $C_{21}H_{20}C_lN_3O_3[M^+]$ 397.1198, found 397.1202. **5f**: mp: 175–176 °C. IR (NaCl): 3440, 3318, 1668, 1629 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 7.2 Hz, CH_3), 2.38 (s, 3H, CH_3-CO), 4.12 (m, 2H, CH_2), 5.32 (s, 1H pyridazine), 6.20 (s, 2H, NH_2), 7.22–7.54 (m, 8H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.88, 33.99, 59.64, 75.93, 125.76, 126.12, 126.86, 127.30, 127.62, 127.91, 129.02, 132.41, 139.62, 141.58, 141.91, 147.38, 150.30, 152.77, 168.85, 196.61; HRMS calcd for $C_{21}H_{19}C_{l2}N_3O_3[M^+]$ 431.0803, found 431.0810. **5g**: mp: 155–156 °C. IR (NaCl): 3460, 3298, 1683, 1633 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 6.6 Hz, CH_3), 2.38 (s, 3H, CH_3-CO), 4.12 (m, 2H, CH_2), 5.30 (s, 1H pyridazine), 6.22(s, 2H, NH_2), 7.22–7.53 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.44, 24.86, 33.96, 59.66, 75.95, 125.76, 126.12, 126.86, 127.30, 127.62, 127.91, 129.02, 132.42, 139.65, 141.59, 141.92, 147.37, 150.30, 152.77, 168.85, 196.60; HRMS calcd. for $C_{21}H_{20}BrN_3O_3[M^+]$ 441.0688, found 441.0693. **5h**: mp: 165–166 °C. IR (NaCl): 3470, 3298, 1688, 1634 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 7.2 Hz, CH_3), 2.37 (s, 3H, CH_3-CO), 4.12 (m, 2H, CH_2), 5.32 (s, 1H pyridazine), 6.20 (s, 2H, NH_2), 7.22–7.54 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.86, 33.95, 59.64, 75.90, 120.52, 125.76, 126.12, 126.86, 127.30, 127.62, 127.91, 129.02, 132.42, 139.65, 141.59, 141.92, 147.37, 150.30, 152.77, 168.88, 196.61; HRMS calcd. for $C_{22}H_{20}N_4O_3[M^+]$ 388.1535, found 388.1542. **5i**: mp: 175–174 °C. IR (NaCl): 3477, 3299, 1688, 1644 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 6.6 Hz, CH_3), 2.36 (s, 3H, CH_3-CO), 3.75 (s, 3H, OCH_3), 4.12 (m, 2H, CH_2), 5.29 (s, 1H pyridazine), 6.20 (s, 2H, NH_2), 7.20–7.51 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.86, 33.95, 55.1, 59.64, 75.90, 120.52, 125.76, 126.12, 126.86, 127.30, 127.62, 127.91, 129.02, 132.42, 141.59, 147.37, 150.30, 159.1, 152.77, 168.88, 196.61; HRMS calcd. for $C_{22}H_{23}N_3O_4[M^+]$ 393.1689, found 393.1696. **5j**: mp: 214–215 °C. IR (NaCl): 3426, 3290, 1664, 1627 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 6.6 Hz, CH_3), 2.38 (s, 3H, CH_3-CO), 3.75 (s, 3H, OCH_3), 4.11 (m, 2H, CH_2), 5.25 (s, 1H, OH), 5.29 (s, 1H pyridazine), 6.20 (s, 2H, NH_2), 7.14–7.51 (m, 9H, ArH); ^{13}C NMR (600 MHz, $CDCl_3$): δ 14.43, 24.85, 33.95, 59.62, 75.95, 125.73, 126.10, 126.86, 127.30, 127.62, 127.91, 129.02, 132.42, 139.65, 141.59, 141.92, 147.37, 150.30, 152.77, 168.85, 196.60; HRMS calcd. for $C_{21}H_{21}N_3O_4[M^+]$ 397.1532, found 379.1540.