JOC The Journal of Organic Chemistry

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Synthesis of α-Aminonitriles with Benzimidazolic and Theophyllinic Backbones Using the Strecker Reaction

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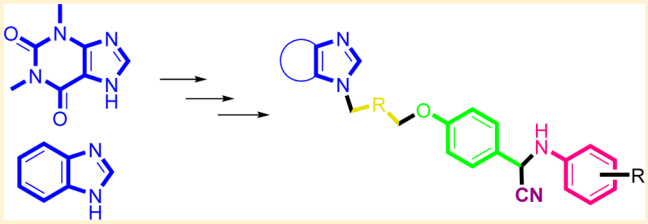
Supporting Information

ABSTRACT: An example of the application of the Strecker reaction in the synthesis of a new class of α-aminonitriles with benzimidazole and theophylline backbones has been developed. For the synthesis of these compounds, first 4-hydroxybenzaldehyde was reacted with 1,3- and 1,5-dibromides/epibromohydrin to produce the corresponding bromo-substituted aldehydes. Then, benzimidazole/theophylline was reacted with the latter to generate the related benzimidazolic/theophyllinic aldehydes. Finally, the Strecker reactions of the synthetic benzimidazolic and theophyllinic aldehydes with different amines afforded the target products.



INTRODUCTION

A large number of nitrile-containing compounds have been widely used as drugs for the treatment of many diseases.[1] There is widespread interest in α-aminonitrile compounds because of their medical utilizations. Several α-aminonitriles have been developed as reversible inhibitors of dipeptidyl peptidase-4 (DPP-4) for the treatment of diabetes.[2] The chemical structures of four important α-aminonitrile-based drugs are shown in Figure 1. As a stimulant drug, amphetaminil has been

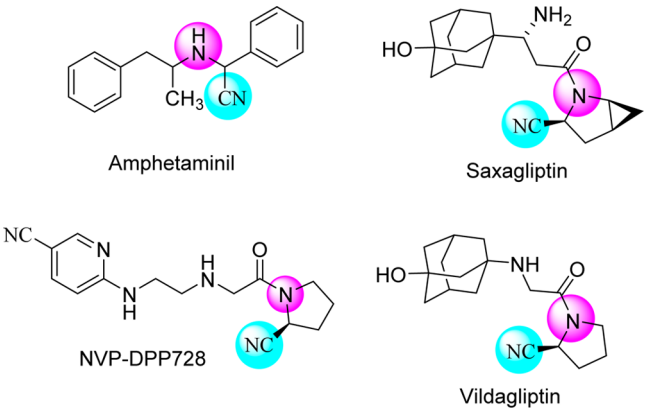


Figure 1. Chemical structures of some α-aminonitrile-based drugs.

used for the treatment of obesity and narcolepsy.[3] Saxagliptin is a new antidiabetic drug that is classified as a potent DPP-4 inhibitor drug.[4] Also, NVP-DPP728 with a slow-binding inhibitory activity related to DPP-4 has been introduced as a new therapeutic approach for treatment of type-2 diabetes.[5] Another most important DPP-4 inhibitor is vildagliptin, which has been used as an efficient antidiabetic drug in recent years.[6] Moreover, several α-aminonitrile products have been isolated from natural sources.[7]

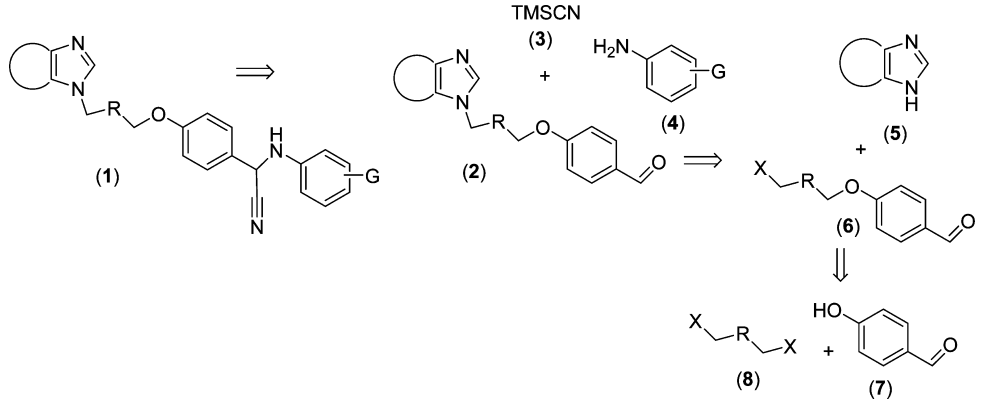
Accordingly, α-aminonitriles are important structural motifs in many biologically active molecules, pharmaceuticals, and natural products. Thus, the development of efficient protocols to construct such moieties and the synthesis of new α-aminonitriles are of great importance to drug discovery.[8] One of the most important strategies for the synthesis of α-aminonitriles is the Strecker reaction, which was discovered in 1850. This reaction is the first multicomponent reaction that involves the one-pot coupling reaction of an amine, an aldehyde, and hydrogen cyanide to afford α-aminonitriles.[9] Since α-aminonitriles are precursors for the synthesis of α-amino acids and many other materials, the Strecker reaction has clinical significance, and for this reason, several modifications of this reaction have been reported in the literature.[10] An efficient one-pot method has been developed for the synthesis of α-aminonitriles by combining aldehydes, amines, and trimethylsilyl cyanide (TMSCN).[11]

In the other hand, theophylline (naturally found in cocoa beans) has been used in therapeutic agents for the treatment of diseases such as chronic obstructive pulmonary disease and asthma. Several important drugs based on theophylline have been developed.[12] Also, benzimidazole is a recognized advantaged structure in medicinal chemistry, showing various biological activities.[13] There is a special interest in the synthesis of new benzimidazole derivatives because of their widespread biological and photophysical properties.

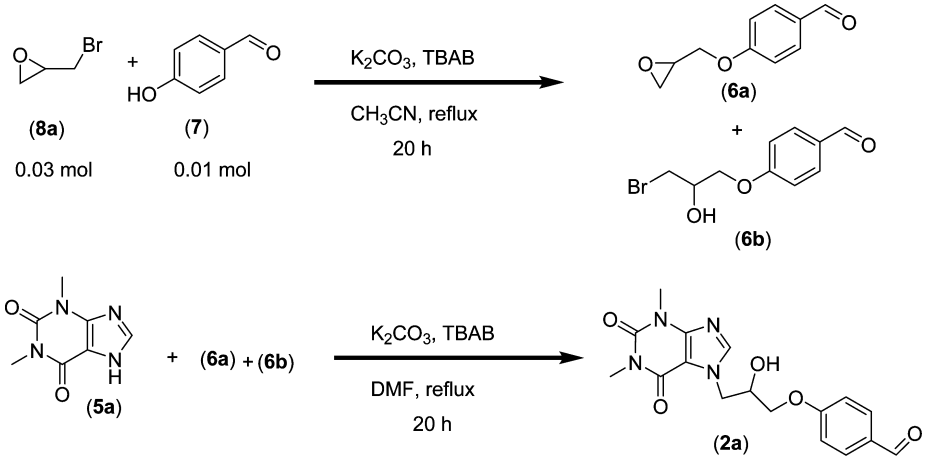
Along this line and in continuation of our previous studies on the synthesis of benzimidazole- and theophylline-based analogues,[13] herein we report an efficient protocol for the synthesis of some novel α-aminonitriles with benzimidazole and theophylline backbones using the Strecker reaction as the key step.

Received: August 26, 2013
Published: October 3, 2013

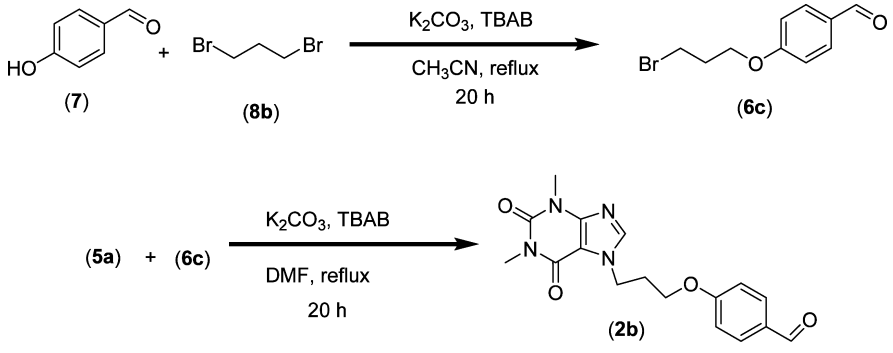
Scheme 1. Retrosynthetic Analysis of the Designed α-Aminonitrile-Based Benzimidazole and Theophylline Compounds



Scheme 2. Synthesis of Theophylline-Based Aldehyde 2a



Scheme 3. Synthetic Route for the Preparation of Theophylline-Based Aldehyde 2b



RESULTS AND DISCUSSION

Our primary retrosynthetic approach for preparation of α-aminonitrile-based benzimidazole and theophylline compounds (**1**) is summarized in Scheme 1. According to this retrosynthesis pathway, the key intermediates are compounds **2**. Thus, our study started with the production of compounds **2**. These molecules are easily obtained from the reaction of benzimidazole or theophylline (**5**) with aldehydes **6**. To prepare aldehydes **6**, 4-hydroxybenzaldehyde (**7**) was treated with epibromohydrin (**8a**)/1,3-dibromopropane (**8b**)/1,5-dibromopropane (**8c**), which gave the corresponding aldehydes **6a**–**d** in high isolated yields.

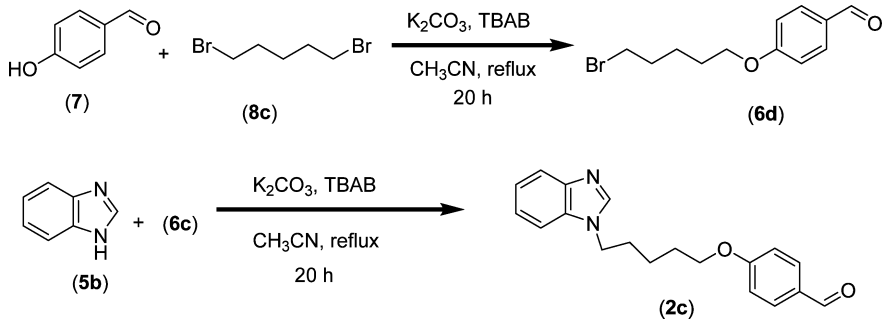
According to our synthetic approach, both products **6a** and **6b** were produced when theophylline was reacted with epibromohydrin. Thus, under the reaction conditions (K_2CO_3, TBAB, CH_3CN, reflux, 20 h), a mixture of **6a** and **6b** was generated. The resulting mixture was used without purification in the next reaction with theophylline (**5a**) to synthesize aldehyde **2a** (Scheme 2).[14]

For the synthesis of theophylline-based aldehyde **2b**, the following synthetic route was used. In the first step, 4-hydroxybenzaldehyde was reacted with 1,3-dibromopropane (**8b**) to produce 4-(3-bromopropoxy)benzaldehyde (**6c**). Then the addition of theophylline to **6c** resulted in the production of aldehyde **2b** in good yield (Scheme 3).

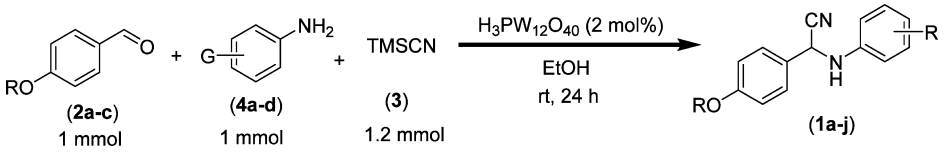
For the synthesis of benzimidazole-based aldehyde **2c**, first 4-hydroxybenzaldehyde was reacted with 1,5-dibromopropane (**8c**) to produce 4-((5-bromopentyl)oxy)benzaldehyde (**6d**),

dx.doi.org/10.1021/jo401890g | J. Org. Chem. 2013, 78, 10902−10908

Scheme 4. Synthetic Route for the Preparation of Benzimidazole-Based Aldehyde 2c



Scheme 5. Strecker Synthesis of Theophylline/Benzimidazole-Based α-Aminonitriles 1a−j



and then benzimidazole was treated with **6d** in order to produce aldehyde **2c** in good yield (Scheme 4).

After the preparation and characterization of the theophylline/benzimidazole-based aldehydes **2a−c**, the Strecker reactions of these aldehydes with different amines were accomplished, and a set of α-aminonitriles with theophylline/benzimidazole backbones were synthesized. Although the synthesis of α-aminonitriles has been widely developed previously, we devised a modified procedure for the Strecker reaction of amines, aldehydes, and TMSCN using tungstophosphoric acid ($H_3PW_{12}O_{40}$) as a catalyst in EtOH solvent. To the best of our knowledge, to date there has been no study of the preparation of α-aminonitriles using $H_3PW_{12}O_{40}$ as a catalyst. Thus, we report an efficient method for the preparation of α-aminonitriles using the Strecker reaction in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ in EtOH at rt (Scheme 5). Our research group has widely used these optimized conditions in organic synthesis.[15] In this study, these conditions were found to be efficient for the synthesis of α-aminonitriles using the Strecker reaction under mild conditions.

We synthesized α-aminonitriles **1a−j** using the procedure shown in Scheme 5, and the results (summarized in Table 1) show that this is an efficient approach for the synthesis of diverse benzimidazolic and theophyllinic α-aminonitriles based on the three-component Strecker reaction of aldehydes, TMSCN, and amines. This facile protocol also can be applied to the synthesis of a wide range of α-aminonitriles by selecting the appropriate aldehydes and amines. As shown in Table 1, the reaction was satisfactorily accomplished with electron-withdrawing and electron-donating groups in the amine component.

CONCLUSIONS

We have elaborated a three-step synthesis of a new class of α-aminonitriles with benzimidazolic and theophyllinic backbones. In these syntheses, the formation of the bromo-substituted aldehydes **6a−d** and their subsequent reaction with benzimidazole and theophylline yielded the related aldehydes **2a−c**. Finally, the acid-catalyzed Strecker reaction of different amines and presynthesized aldehydes **2a−c** with TMSCN led to the formation of the target molecules **1a−j** in good to excellent yields.

EXPERIMENTAL SECTION

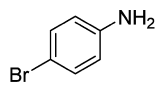
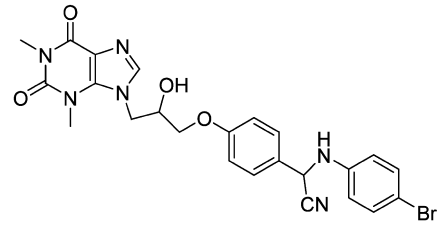
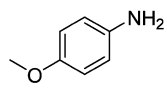
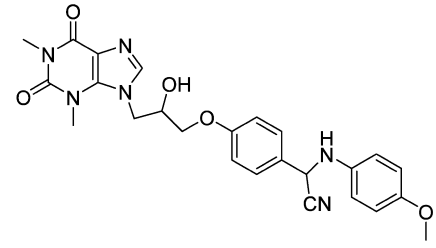
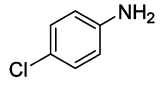
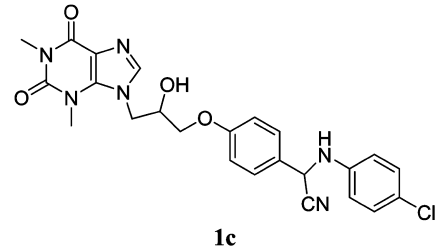
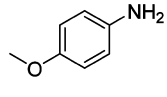
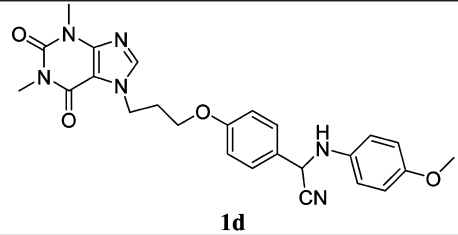
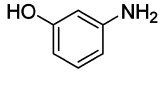
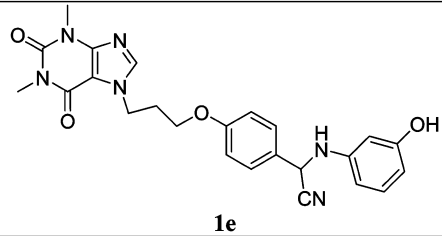
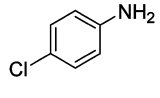
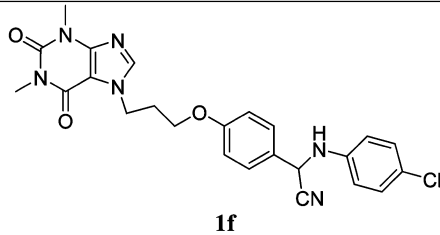
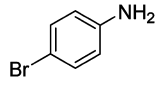
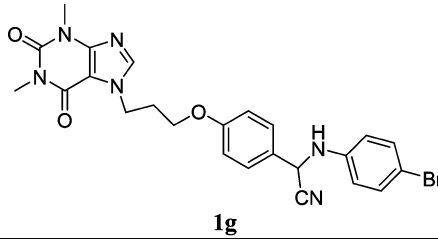
General Experimental Details. All of the commercial reagents and solvents were used without further purification. Melting points were determined in open capillary tubes. FT-IR spectroscopy was employed for characterization of the synthesized compounds using film KBr pellet techniques. NMR spectra were acquired in DMSO-d_6 with tetramethylsilane (TMS) as the internal standard. The sample was analyzed by GC/MS for mass spectrometry and a microanalyzer for elemental analyses. Reaction monitoring was accomplished by TLC on silica gel plates. Column chromatography was carried out on columns of silica gel 60 (70−230 mesh).

*4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-2-hydroxypropoxy)benzaldehyde (**2a**). Synthesis of **6a** and **6b**.* In a double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture of 4-hydroxybenzaldehyde (0.03 mol), K_2CO_3 (4.14 g, 0.03 mol), epibromohydrin (4.92 g, 0.036 mol), and a catalytic amount of tetrabutylammonium bromide (TBAB, 0.1 g) was dissolved in MeCN (40 mL). Then the mixture was heated to reflux for 10 h (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in $CHCl_3$ (150 mL) and washed with H_2O (2 × 150 mL). The organic layer was dried (Na_2SO_4, 10 g) and concentrated to afford the crude product consisting of a mixture of **6a** and **6b**. The crude product was then used without any further purification for the synthesis of **2a** according to the procedure described below.

*Synthesis of **2a**.* To a double-necked round-bottom flask (100 mL) equipped with a condenser was added a mixture consisting of theophylline (0.01 mol, 1.8 g), K_2CO_3 (1.38 g, 0.01 mol), bromoalcohols **6a** and **6b** (0.015 mol), and a catalytic amount of TBAB (0.1 g) in DMF (40 mL). The solution was refluxed until TLC monitoring indicated no further improvement in the reaction (8−10 h). After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (2 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude material was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:2), R_f = 0.5], and the product was obtained in 70% yield (2.5 g). IR (KBr): ν = 3207, 2851, 2365, 1682, 1640, 1737, 1590, 1354, 1157 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ 3.32 (s, 3H), 3.51 (s, 3H), 4.00−4.06 (m, 2H), 4.38−4.44 (m, 2H), 4.60−4.65 (m, 1H), 6.93−7.79 (m, 5H), 8.06 (s, 1H), 9.80 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 28.12, 31.13, 80.1, 84.3, 107.1, 115.3, 122.0, 131.2, 142.3, 151.3, 154.2,

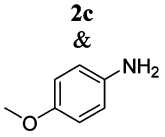
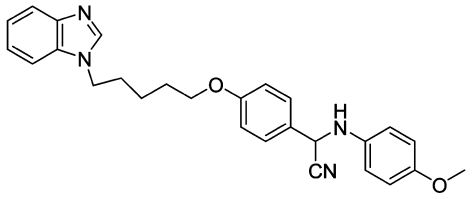
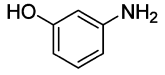
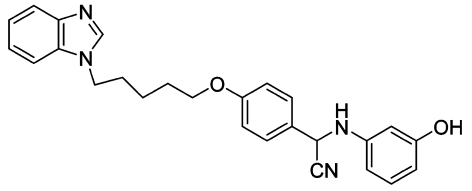
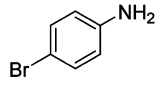
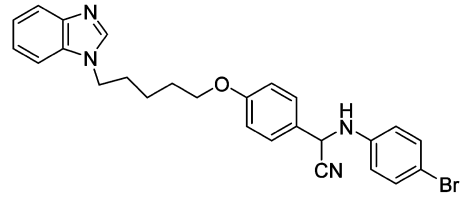
dx.doi.org/10.1021/jo401890g | J. Org. Chem. 2013, 78, 10902−10908

Table 1. Products of the Three-Component Strecker Reactions of Aldehydes 2a−c, TMSCN, and Amines[a]

Entry	Aldehyde & Amine	Product	Yield (%)[b]
1	**2a** & 	 **1a**	88
2	**2a** & 	 **1b**	90
3	**2a** & 	 **1c**	91
4	**2b** & 	 **1d**	94
5	**2b** & 	 **1e**	90
6	**2b** & 	 **1f**	90
7	**2b** & 	 **1g**	92

dx.doi.org/10.1021/jo401890g | J. Org. Chem. 2013, 78, 10902−10908

Table 1. continued

Entry	Aldehyde & Amine	Product	Yield (%)[b]
8	**2c** & 	 **1h**	92
9	**2c** & 	 **1i**	89
10	**2c** & 	 **1j**	92

[a]Reagents and conditions: aldehyde **2** (1 mmol), TMSCN (1.2 mmol), amine (1 mmol), $H_3PW_{12}O_{40}$ (0.04 g, 2 mol %), and EtOH (5 mL). [b]Isolated yields.

157.0, 160.2. Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63. Found: C, 57.07; H, 5.12; N, 15.71.

*4-(3-Bromopropoxy)benzaldehyde (**6c**).* In double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of *p*-hydroxybenzaldehyde (0.02 mol, 2.44 g), 1,3-dibromopropane (0.06 mol), K_2CO_3 (2.76 g, 0.02 mol), and a catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 10 h. After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:2), R_f = 0.6], giving a white solid in 80% yield (3.9 g). IR (KBr): ν = 3150, 2900, 2790, 1697, 1730, 1450, 1589, 1154, 1260, 670 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.13 (m, 2H), 3.50 (t, J = 5 Hz, 2H), 4.02 (t, J = 5 Hz, 2H), 7.20−7.80 (m, 4H), 9.87 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 29.9, 32.9, 67.0, 106.8, 114.4, 114.9, 122.0, 128.3, 132.0, 190.2. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.48; H, 4.63.

*4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-propoxy)benzaldehyde (**2b**).* In a double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of 4-(3-bromopropoxy)benzaldehyde (0.01 mol, 2.43 g), theophylline (0.01 mol, 1.8 g), K_2CO_3 (1.38 g, 0.01 mol), and a catalytic amount of TBAB (0.1 g) in DMF (50 mL) was refluxed for 10 h. After the mixture was cooled, the solvent was evaporated under vacuum, and then the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:2), R_f = 0.6], giving a white solid in 70% yield (2.4 g). IR (KBr): ν = 3217, 2854, 2360, 1672, 1640, 1735, 1590, 1350, 1150 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.34−2.44 (m, 2H), 3.37 (s, 3H), 3.59 (s, 3H), 4.00 (t, J = 5 Hz, 2H), 4.48 (t, J = 5 Hz, 2H), 6.51−7.80 (m, 4H), 8.08 (s, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 29.0, 30.1, 30.7, 43.0, 64.1, 107.0, 114.9, 128.5, 131.9, 141.0, 148.4, 151.3, 154.8, 165.2, 191.0. Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.71; H, 5.35; N, 16.41.

*4-((5-Bromopentyl)oxy)benzaldehyde (**6d**).* In double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of *p*-hydroxybenzaldehyde (0.02 mol, 2.44 g), 1,5-dibromopropane (0.06 mol), K_2CO_3 (2.76 g, 0.02 mol), and a catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 10 h. After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$, (150 mL) and washed with water (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:2), R_f = 0.7], giving white crystals in 75% yield (2.03 g). IR (KBr): ν = 3155, 2920, 2795, 1690, 1735, 1450, 1581, 1250, 1150, 665 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 1.55−1.61 (m, 2H), 1.81−1.97 (m, 4H), 3.62 (t, J = 5, 2H), 4.06 (t, J = 5, 2H), 7.18−7.88 (m, 4H), 9.86 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 24.0, 28.5, 32.9, 33.8, 68.7, 114.2, 114.9, 130.2, 190.6. Anal. Calcd for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58. Found: C, 53.19; H, 5.62.

*4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-propoxy)benzaldehyde (**2c**).* In a double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of benzimidazole (0.01 mol, 1.18 g), preformed compound **6d** (0.012 mol), K_2CO_3 (1.38 g, 0.01 mol), and a catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 7 h. After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:1), R_f = 0.7] giving white crystals in 80% yield (2.15 g). IR (KBr): ν = 3125, 2910, 2815, 1690, 1737, 1450, 1581, 1256, 1115 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 1.58−1.64 (m, 2H), 1.83−1.97 (m, 4H), 3.99 (t, J = 5 Hz, 2H), 4.26 (t, J = 5 Hz, 2H), 6.93−7.45 (m, 4H), 8.27 (s, 1H) 9.87 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 23.3, 29.3, 29.6, 52.3, 66.7, 110.0, 114.9,

dx.doi.org/10.1021/jo401890g | J. Org. Chem. 2013, 78, 10902−10908

119.9, 123.0, 128.5, 131.9, 132.5, 143.8, 144.1, 165.2, 192. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.05; H, 6.58; N, 9.12.

General Procedure for the Synthesis of α-Aminonitrile-Based Benzimidazole/Theophylline Compounds 1a−j. A mixture of aldehyde **2a−c** (1 mmol), aniline derivative (1 mmol), TMSCN (1.2 mmol), and tungstophosphoric acid (0.04 g, 2 mol %) in EtOH (5 mL) was stirred at room temperature for 24 h. The completion of the reaction was confirmed by TLC (eluent: EtOAc/MeOH). Then the precipitated product was filtered and washed with water (2 × 10 mL) and ethanol (10 mL) to afford the pure product.

*2-((4-Bromophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)-acetonitrile (**1a**).* Yield 88% (0.47 g), white crystals, mp 186 °C. IR (KBR): ν = 3409, 2923, 2260, 1697, 1550, 1512, 1242, 946 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 3.32 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 4.00−4.06 (m, 4H, CH_2), 4.38−4.44 (m, 2H), 4.61 (s, 1H), 6.93−7.79 (m, 9H), 8.76 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: m/z 538.12 (18, M^+). Anal. Calcd for $C_{24}H_{23}BrN_6O_4$: C, 53.44; H, 4.30; N, 15.58. Found: C, 53.55; H, 4.27; N, 15.65.

*2-(4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)-2-((4-methoxyphenyl)amino)-acetonitrile (**1b**).* Yield 90% (0.44 g), white crystals, mp 190 °C. IR (KBr): ν = 3440, 3317, 2954, 2839, 1697, 1651, 1550, 1512, 1473, 1234, 1180, 825 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 3.32 (s, 3H), 3.51 (s, 3H), 3.82 (s, 3H), 4.20−4.32 (m, 4H), 4.38−4.44 (m, 2H), 4.61 (s, 1H), 7.20−7.65 (m, 10H), 8.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: m/z 490.23 (15, M^+). Anal. Calcd for $C_{25}H_{26}N_6O_5$: C, 61.22; H, 5.34; N, 17.13. Found: C, 61.30; H, 5.27; N, 17.20.

*2-((4-Chlorophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)-acetonitrile (**1c**).* Yield 91% (0.45 g), white crystals, mp 190 °C. IR (KBr): ν = 3442, 3317, 2950, 2837, 1692, 1651, 1550, 1514, 1473, 1234, 1180, 830 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 3.36 (s, 3H), 3.59 (s, 3H), 4.00−4.06 (m, 4H), 4.58−4.79 (m, 2H), 4.96 (s, 1H), 6.93−7.79 (m, 10H), 8.58 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.9, 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.5. MS: m/z 494.17 (19, M^+). Anal. Calcd for $C_{24}H_{23}ClN_6O_4$: C, 58.24; H, 4.68; N, 16.98. Found: C, 58.35; H, 4.57; N, 17.01.

*2-(4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,4,5,6-hexahydro-9H-purin-9-yl)propoxy)phenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**1d**).* Yield 94% (0.44 g), white crystals, mp 215 °C. IR (KBr): ν = 3375, 2881, 2356, 1689, 1649, 1612, 1550, 1342, 1288, 1249, 1184, 1817, 769 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.34−2.44 (m, 2H), 3.34 (s, 3H), 3.53 (s, 3H), 3.74 (s, 3H), 3.97 (t, J = 5.0 Hz, 2H), 4.46 (t, J = 5.0 Hz, 2H), 4.85 (s, 1H), 6.85−7.84 (m, 9H), 8.39 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.9, 29.7, 29.9, 30.0, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: m/z 474.21 (12, M^+). Anal. Calcd for $C_{25}H_{26}N_6O_4$: C, 63.28; H, 5.52; N, 17.71. Found: C, 63.36; H, 5.57; N, 17.79.

*2-(4-(3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propoxy)phenyl)-2-((3-hydroxyphenyl)amino)acetonitrile (**1e**).* Yield 90% (0.41 g), white crystals, mp 175 °C. IR (KBr): ν = 3379, 2885, 2360, 1697, 1651, 1612, 1550, 1342, 1288, 1249, 1180, 1817, 763 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.31−2.45 (m, 2H), 3.48 (s, 3H), 3.54 (s, 3H), 4.00 (t, J = 5 Hz, 2H), 4.48 (t, J = 5 Hz, 2H), 4.85 (s, 1H), 5.10 (s, 1H), 6.91−7.84 (m, 10H), 8.14 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.6, 29.5, 29.9, 30.9, 44.1, 53.6, 64.0, 68.2, 106.8, 114.2, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 174.8, 179.1. MS: m/z 460.17 (15, M^+). Anal. Calcd for $C_{24}H_{24}N_6O_4$: C, 62.60; H, 5.25; N, 18.25. Found: C, 62.68; H, 5.29; N, 18.31.

*2-((4-Chlorophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propoxy)phenyl)acetonitrile (**1f**).* Yield 90% (0.43 g), white crystals, mp 250 °C. IR (KBr): ν = 3369, 2889, 2364, 1687, 1652, 1618, 1557, 1345, 1289, 1259, 1180, 1827, 768 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.34−2.44 (m, 2H), 3.24 (s, 3H), 3.46 (s, 3H), 3.94 (t, J = 7.5 Hz, 2H), 4.46 (t, J = 7.5, 2H), 4.81 (s, 1H), 6.60−7.83 (m, 10H), 8.05 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.4, 29.8, 29.9, 30.0, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 166.5, 174.8. MS: m/z 478.18 (11, M^+). Anal. Calcd for $C_{24}H_{23}ClN_6O_3$: C, 60.19; H, 4.84; N, 17.55. Found: C, 60.19; H, 4.84; N, 17.55.

*2-((4-Bromophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propoxy)phenyl)acetonitrile (**1g**).* Yield 92% (0.48 g), white crystals, mp 175 °C. IR (KBr): ν = 3317, 2954, 2360, 1697, 1651, 1589, 1542, 1512, 1404, 1242, 1180, 1072, 825 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 2.28−2.33 (m, 2H), 3.34 (s, 3H), 3.53 (s, 3H), 3.97 (t, J = 5, 2H), 4.46 (t, J = 5, 2H), 4.95 (s, 1H), 5.34 (s, 1H), 673−7.45 (m, 10H), 8.04 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.0, 29.5, 29.9, 30.9, 36.8, 44.2, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 174.8, 179.1. MS: m/z 522.12 (9, M^+). Anal. Calcd for $C_{24}H_{23}BrN_6O_3$: C, 55.08; H, 4.43; N, 16.06. Found: C, 55.12; H, 4.48; N, 16.14.

*2-(4-((5-(1H-Benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**1h**).* Yield 92% (0.40 g), white crystals, mp 200 °C. IR (KBr): ν = 3440, 3139, 2923, 2351, 1604, 1512, 1249, 108, 817 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 1.69−1.84 (m, 6H), 3.75 (s, 3H), 3.97 (t, J = 5.0 Hz, 2H), 4.46 (t, J = 5.0 Hz, 2H), 4.81 (s, 1H), 4.95 (s, 1H), 6.95−7.78 (m, 12H), 8.81 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 22.5, 28.0, 28.7, 44.8, 48.5, 67.41, 111.5, 114.3, 114.4, 114.5, 114.7, 115.3, 117.5, 119.9, 122.5, 123.3, 123.7, 128.5, 130.1, 132.5, 138.2, 139.7, 142.8, 152.2, 158.7, 161.0. MS: m/z 440.20 (19, M^+). Anal. Calcd for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.68; H, 6.46; N, 12.79.

*2-(4-((5-(1H-Benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((3-hydroxyphenyl)amino)acetonitrile (**1i**).* Yield 94% (0.40 g), white crystals, mp 230 °C. IR (KBr): ν = 3446, 3134, 2927, 2361, 1608, 1522, 1249, 1108, 820 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 1.51−2.04 (m, 6H), 3.97 (t, J = 5.0 Hz, 2H), 4.46 (t, J = 5.0 Hz, 2H), 4.90 (s, 1H), 5.15 (s, 1H), 6.73−7.67 (m, 12H), 8.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 22.5, 28.0, 28.7, 44.8, 48.5, 67.41, 111.5, 114.3, 114.4, 114.5, 114.7, 115.3, 117.5, 122.1, 123.3, 128.5, 130.1, 131.7, 132.5, 138.2, 139.7, 142.8, 161.0. MS: m/z 426.22 (17, M^+). Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14. Found: C, 73.31; H, 6.21; N, 13.20.

*2-(4-((5-(1H-Benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((4-bromophenyl)amino)acetonitrile (**1j**).* Yield 91% (0.44), white crystals, mp 156 °C. IR (KBr): ν = 3438, 3136, 2925, 2349, 1614, 1518, 1259, 1108, 827 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ 1.69−1.84 (m, 6H), 3.98 (t, J = 5.0, 2H), 4.48 (t, J = 5.0 Hz, 2H), 4.89 (s, 1H), 5.84 (s, 1H), 6.73−7.67 (m, 12H), 8.33 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ 27.9, 29.7, 29.9, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 114.5, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: m/z 488.14 (14, M^+). Anal. Calcd for $C_{26}H_{25}BrN_4O$: C, 63.81; H, 5.15; N, 11.45. Found: C, 63.88; H, 5.19; N, 11.50.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The financial support from the Research Councils of Shiraz University is gratefully acknowledged.

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