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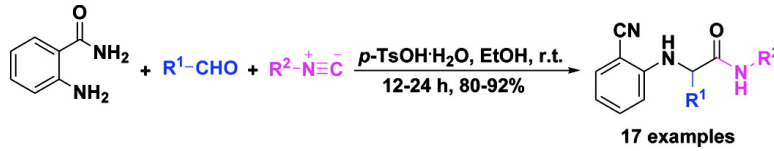

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Novel Isocyanide-Based Three-Component One-Pot Synthesis of Cyanophenylamino-acetamide Derivatives

Ahmad Shaabani,* Ali Maleki, Hamid Mofakham, and Hamid Reza Khavasi

Department of Chemistry, Shahid Beheshti University, P.O. Box 19396-4716, Tehran, Iran

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A one-pot multicomponent synthesis of a novel class of cyanophenylamino-acetamides through the conversion of primary amides to the corresponding nitriles, starting from simple and readily available inputs including 2-aminobenzamide, an aldehyde, and an isocyanide in the presence of *p*-toluenesulfonic acid as a catalyst, in excellent yields at room temperature in ethanol as a green reaction medium is described.

Introduction

Multicomponent reactions (MCRs) are of great interest to organic chemists for several reasons. They are extensively used in medicinal chemistry as fast and selective methods for the synthesis of large libraries of organic molecules because the products are formed in a single step by simultaneous reaction of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component through a chain of consecutive elementary transformations.[1] Because of the unique reactivity of the isocyanide functional group, isocyanide-based multicomponent reactions (I-MCRs) are among the most versatile, in terms of the number and variety of compounds which can be generated.[1]

Aromatic *o*-aminonitriles are versatile synthons[2] for the synthesis of biologically active and pharmaceutically important compounds such as pyrimidines,[3] quinazolinones,[4] quinazolinediones,[5] and other fused nitrogen-containing heterocycles.

Furthermore, the conversion of the primary carboxamide functionality into the cyano functional group is an important process that has extensive utility in organic synthesis[6] because it is useful for the introduction of nitrogen into organic molecules for the activation of adjacent C−H bonds and for efficient conversion into other functional groups, such as amines and ketones.[7] The dehydration of primary amides to nitriles has long relied upon the use of strong dehydrating agents, such as P_2O_5,[8] $SOCl_2$,[9] or dimethylzirconocene.[10] Such transformations often require high temperatures and lead to multiple byproducts, depending on the functional groups present in the starting amide.

In our continuing interest in I-MCRs,[11] herein, we report a hitherto unknown reaction for the conversion of primary amides to the corresponding nitriles, which affords a novel class of cyanophenylamino-acetamides **4a**−**q** from three-component condensation reaction between 2-aminobenzamide **1**, an aldehyde **2**, and an isocyanide **3** in the presence of *p*-toluenesulfonic acid (*p*-TsOH. H_2O) as a catalyst in high yields in ethanol at room temperature (Scheme 1).

Results and Discussion

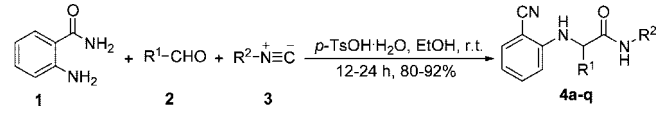
In a pilot experiment, 2-aminobenzamide, benzaldehyde, and cyclohexyl isocyanide in EtOH were stirred at room temperature using *p*-toluenesulfonic acid as a catalyst. The progress of the reaction was monitored by TLC. After completion of the reaction after 12 h, an aqueous workup afforded 2-(2-cyanophenylamino)-*N*-cyclohexyl-2-phenylacetamide **4a** in 80% yield.

A variety of aldehydes and isocyanides were employed under similar circumstances to evaluate the substrate scope of this reaction. The results are shown in Table 1. As anticipated from our original results, these reactions proceeded very cleanly at room temperature and no undesirable side reactions were observed.

The aromatic aldehydes carrying both electron-withdrawing and electron-releasing substituents were also converted to their corresponding cyanophenylamino-acetamide derivatives in relatively similar times and yields (entries 2−8). It is noteworthy that the reactions of halo-substituted benzaldehydes proceeded with the expected mechanism and exhibit excellent yields (entries 9−14). The thiophene-2-carbaldehyde, as a heteroaromatic aldehyde, was used in this reaction and gave very good yields (entries 15 and 16). We have also examined the aliphatic aldehyde to survey the scope and generality of this reaction; thus 3-phenylpropanal was reacted with 2-aminobenzamide and cyclohexyl isocyanide successfully (entry 17).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Two substituents in the products can be varied independently of each other. Representative examples of this reaction are shown in Figure 1.

Scheme 1. Synthesis of Cyanophenylamino-acetamides **4a**−**q**



* To whom correspondence should be addressed. Phone: +98-21-29902800. Fax: +98-21-22431663. E-mail: a-shaabani@cc.sbu.ac.ir.

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Table 1. Cyanophenylamino-acetamide Derivatives **4a**−**q** Produced from the MCRs of 2-Aminobenzamide

entry	aldehyde	isocyanide	product	time (h)	yield[a] (%)
1	benzaldehyde	cyclohexyl	**4a**	12	80
2	3-nitrobenzaldehyde	cyclohexyl	**4b**	12	85
3	3-nitrobenzaldehyde	*tert*-butyl	**4c**	14	90
4	3-nitrobenzaldehyde	1,1,3,3-tetramethylbutyl	**4d**	18	92
5	3-nitrobenzaldehyde	benzyl	**4e**	12	85
6	3-nitrobenzaldehyde	2,6-dimethylphenyl	**4f**	24	80
7	4-methylbenzaldehyde	cyclohexyl	**4g**	14	82
8	4-methoxylbenzaldehyde	cyclohexyl	**4h**	15	80
9	3-bromobenzaldehyde	cyclohexyl	**4i**	13	90
10	3-bromobenzaldehyde	*tert*-butyl	**4j**	14	85
11	4-bromobenzaldehyde	cyclohexyl	**4k**	14	88
12	4-bromobenzaldehyde	*tert*-butyl	**4l**	16	85
13	4-fluorobenzaldehyde	cyclohexyl	**4m**	14	85
14	4-fluorobenzaldehyde	*tert*-butyl	**4n**	16	90
15	thiophene-2-carbaldehyde	cyclohexyl	**4o**	17	86
16	thiophene-2-carbaldehyde	*tert*-butyl	**4p**	20	83
17	3-phenylpropanal	cyclohexyl	**4q**	22	80

[a] Isolated yield.

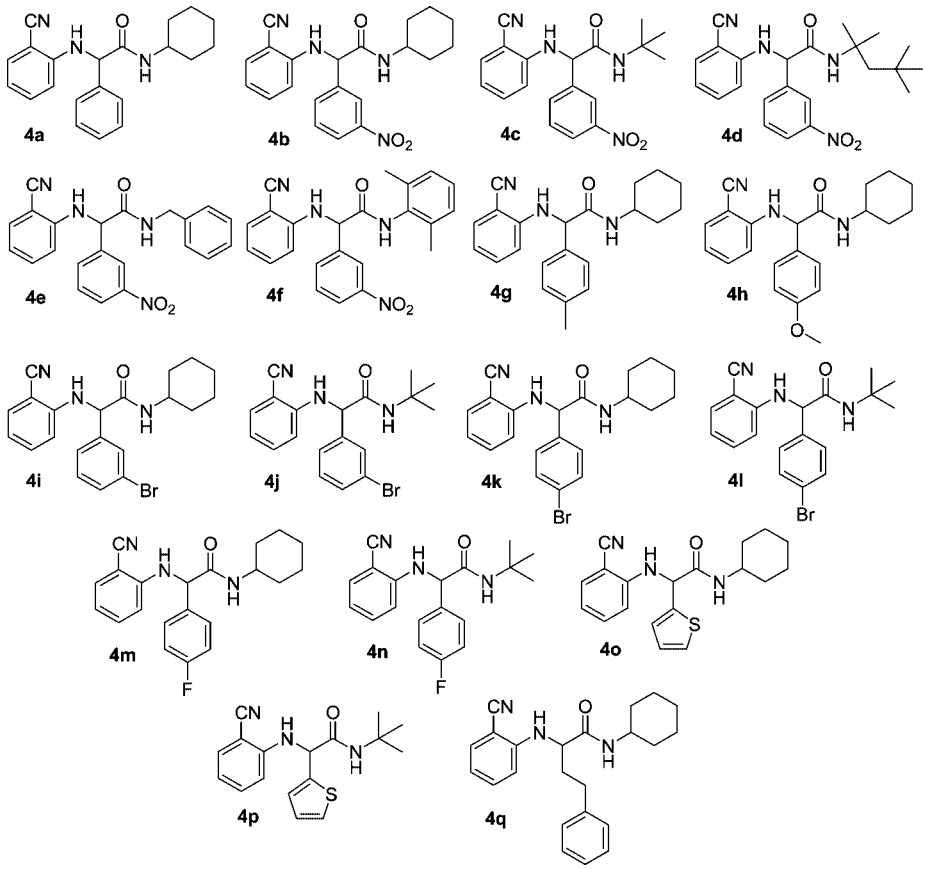
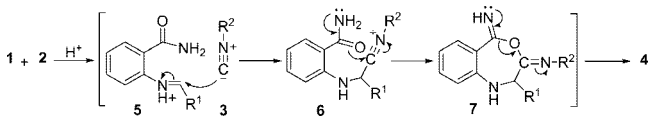


Figure 1. Structure of products **4a**−**q**.

Scheme 2. Possible Mechanism for the Formation of Products **4a**−**q**



Next, we decided to extend this reaction to ketones; however, 2,3-dihydroquinazolin-4(1*H*)-one derivatives were generated, and nucleophilic attack by isocyanide did not occur.

The possible mechanism for the formation of products **4a**−**q** is shown in Scheme 2. It is conceivable that the initial event is the formation of iminium **5** from 2-aminobenzamide **1** and an aldehyde **2**. On the basis of the well-established chemistry of reaction of isocyanides with imines,[1] intermediate **6** was produced by nucleophilic attack of isocyanide **3** to activated iminium **5**. Then, intramolecular nucleophilic attack of amide group from oxygen side to the activated nitrile moiety yields intermediate **7**. Finally, ring opening of intermediate **7** leads to the formation of product **4**.

Finally, the structure of the product **4n** was confirmed unambiguously by single-crystal X-ray analysis (see the Supporting Information and Figure 2).[12]

Conclusions

In summary, we have developed a novel, mild, and straightforward procedure for the synthesis of a new class

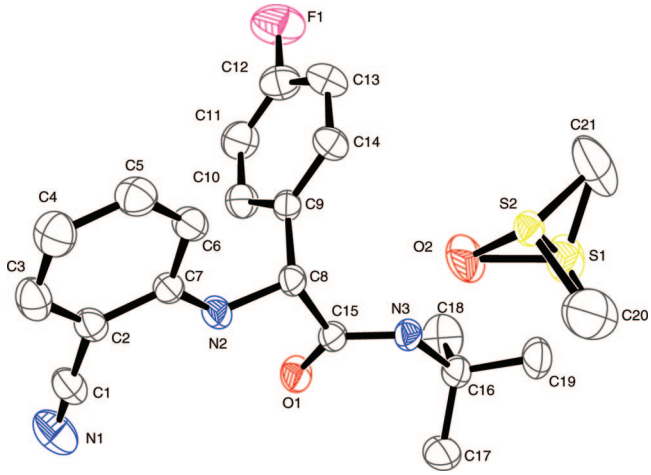


Figure 2. ORTEP representation of compound **4n**.

of substituted cyanophenylamino-acetamide derivatives from three-component condensation reaction between 2-aminobenzamide, an aldehyde, and an isocyanide in the presence of *p*-toluenesulfonic acid as a catalyst in excellent yields at room temperature. In this reaction, for the first time, an interesting rearrangement including a seven-member ring intermediate occurs during the proposed mechanism to yield nitrile functionality. This novel reaction can be regarded as an efficient approach for the conversion of primary amides to the corresponding nitriles and preparation of pharmaceutically relevant cyanophenylamino-acetamide derivatives.

Experimental Section

Typical Procedure for the Synthesis of 2-(2-Cyanophenylamino)-*N*-cyclohexyl-2-phenylacetamide (4a). To a solution of 2-aminobenzamide (0.136 g, 1 mmol), benzaldehyde (0.106 g, 1 mmol), and cyclohexyl isocyanide (0.109 g, 1 mmol) in 3 mL of ethanol was added *p*-TsOH. H_2O (0.095 g, 0.5 mmol). The resulting mixture was stirred for 12 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2/1), the product was precipitated by addition of 10 mL of water. The precipitate was filtered off and washed with 5 mL of 5% sodium hydroxide solution and then with 15 mL of water. The residue was crystallized from acetone to give **4a** as colorless crystals (0.266 g, 80%). mp: 142−144 °C. IR (KBr) cm^{-1}: 3400, 3282, 3071, 2932, 2847, 2210, 1642, 1609, 1556, 1512, 1460, 1320. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 1.00−2.00 (10H, m, 5CH_2 of cyclohexyl), 3.50 (1H, m, CH of cyclohexyl), 5.14 (1H, d, J = 6.7 Hz, CH), 6.14 (1H, d, J = 6.6 Hz, NH), 6.46 (1H, d, J = 8.4 Hz, H−Ar), 6.67 (1H, t, J = 7.3 Hz, H−Ar), 7.26−7.51 (7H, m, H−Ar), 8.28 (1H, d, J = 7.3 Hz, NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 24.7, 24.8, 25.5, 32.4, 32.6, 48.4 (carbons of cyclohexyl), 59.4 (CH), 96.1 (CN), 112.4, 117.5, 118.0, 127.0, 128.3, 129.1, 133.4, 134.9, 139.0, 148.5 (C−Ar), 169.0 (CO). MS *m*/*z*: 334 (M^+ + 1, 5), 225 (2), 207 (100), 129 (35), 102 (16), 77 (12), 56 (14), 44 (10). Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; found C, 75.52; H, 6.98; N, 12.44.

Acknowledgment. We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supporting Information Available. Experimental procedures, mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4a**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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