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A Practical Way to Prepare Isobutyronitrile Amides through Reactions between Carboxylic Acids and Azobisisobutyronitrile

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Abstract: A practical and efficient synthesis of *N*-isobutyronitrile amides has been achieved through the direct condensation of carboxylic acid and azobisisobutyronitrile (AIBN). Carboxylic acids bearing variously substituted phenyl rings and cinnamic or phenylpropiolic acids were employed to furnish both tertiary and secondary isobutyronitrile amides in moderate to high yields. A radical pathway was proposed. The methodology presented here requires no catalysts and additives, and represents the first practical approach to a variety of valuable amides containing the isobutyronitrile structural unit.

Keywords: azobisisobutyronitrile; carboxylic acids; cinnamic acids; isobutyronitrile amides; phenylpropiolic acids

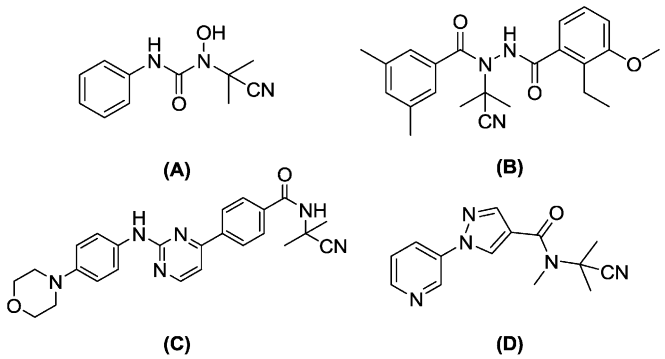

Figure 1. Several useful aromatic amides that contain an *N*-isobutyronitrile structure unit.

Aromatic amides are one of the most important molecular building blocks that are widely found in naturally occurring compounds.[1] Over the past decades, considerable attention has been paid to exploration of their synthesis as well as biological applications, because of the amphipathic arenes that are found in helical oligomers.[2] Aromatic amides containing an isobutyronitrile substituent on the amide nitrogen are essential structural motifs of a class of pharmaceutical molecules that display significant biological activities. For example, compound **A** (Figure 1), a simple *N*-isobutyronitrile amide analogue, has been found to inhibit the formation of thrombus in arterioles by 14 percent;[3] the *N*-isobutyronitrile bis-amide **B** is a reagent widely used in biological research. In addition, compounds **C** and **D** also show great potential for applications in the pesticide field.[4] Obviously, all these compounds have the same structural unit of an *N*-isobutyronitrile aromatic amide. However, amongst the known protocols to prepare aromatic amides, the synthesis of *N*-isobutyronitrile amides is very limited.

Traditionally, ammonia is used as the nitrogen source for amide synthesis in the chemical industry.[5] However, the sequential introduction of an *N*-isobutyronitrile moiety to the amide requires multiple-step reactions and tedious operating procedures, and hence it is quite energy-consuming. Thus, these methodologies are unpractical for large-scale industrial applications. Although a synthesis of *N*-isobutyronitrile benzamide from benzoyl 2-amino-2-methylpropanenitrile was revealed by Granger and co-workers in 1960, the high cost and poor availablility of the starting material 2-amino-2-methylpropanenitrile has largely limited this protocol for any practical applications.[6] Therefore, it becomes urgent to develop a practical, effective approach to useful *N*-isobutyronitrile amide

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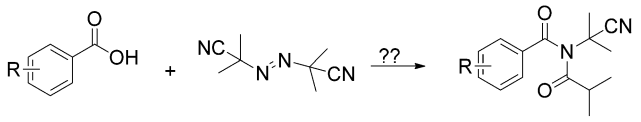


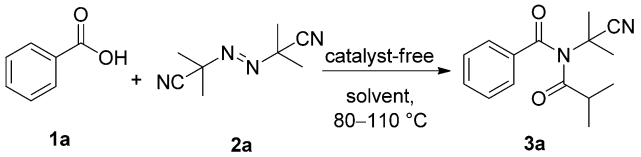
Scheme 1. A plausible route to *N*-isobutyronitrile benzamide.

compounds from simple, inexpensive starting materials.

Azobisisobutyronitrile (AIBN), a molecule containing both an azo group and an isobutyronitrile unit, is a well-known radical initiator for polymer synthesis. However, it has been scarcely exploited as a nitrogen source in synthetic chemistry. We envisioned that the *N*-isobutyronitrile motif could be introduced while using AIBN as a nitrogen source for the amide forming reaction as proposed in Scheme 1. Herein, we report for the first time a catalyst-free, inexpensive approach to a wide range of *N*-isobutyronitrile benzamides and other relevant analogues resulting from direct condensations of carboxylic acids with AIBN.

In our initial attempt, benzoic acid and AIBN were chosen to react in toluene at 120 °C for 12 h. To our delight, the desired isobutyronitrile amide **3a** was isolated in 44% yield (entry 1, Table 1). In contrast, we also tested the same reaction in the presence of catalysts, but poorer conversions were obtained in all cases. Therefore, we focused on an optimization of the conditions for the direct condensation of benzoic acid and AIBN without a catalyst. Remarkably, it turned out that the solvent plays a crucial role in determining reactivity, and after screening of a variety of solvents (Table 1), cyclohexane was found to be most effective. Thus, when benzoic acid (0.3 mmol) and AIBN (0.6 mmol) were employed in the reaction using cyclohexane as solvent under an argon atmosphere for 12 h at 80 °C, a yield of **3a** as high as 96% (entry 11, Table 1) was achieved. Changing the amount of **2a** could influence the catalytic effect (entries 12 and 13, Table 1) and 2 equiv. is the best in view of the cost of the reaction. In addition, DMSO (dimethyl sulfoxide), DMF (*N*,*N*-dimethylformamide), ethanol and PEG-400 were investigated in the reaction as the solvents and the desired product **3a** could not be obtained.

Table 1. Modification of the typical reaction conditions.[a]



1a **2a** **3a**

Entry	Solvent	Temp. [°C]	Yield [%][b]
1	toluene	110	44
2	ethanol	80	37
3	DMSO	100	NR
4	dioxane	100	10
5	CH_2ClCH_2Cl	80	68
6	1,4-xylene	100	78
7	$CHCl_2CH_2Cl$	100	27
8	acetonitrile	80	50
9	mesitylene	100	77
10	*n*-hexane	80	94
11	cyclohexane	80	96
12[c]	cyclohexane	80	85
13[d]	cyclohexane	80	97

[a] *Reaction conditions:* Benzoic acid **1a** (0.3 mmol), AIBN **2a** (0.6 mmol), solvent (2 mL), 12 h, 80–110 °C, Ar.
[b] Isolated yield. NR: no reaction.
[c] Ratio of **1a/2a** = 1/1.5.
[d] Ratio of **1a/2a** = 1/3.

With the optimized conditions in hand, we next explored the scope of substrates and the results are illustrated in Table 2. It was found that various substituted benzoic acids are tolerated and all furnished the products in good to excellent yields. For most of the mono-substituted substrates such as 4-methyl-, 4-*tert*-butyl-, 4-fluoro- and 4-acetylbenzoic acids, high yields of up to 99% were obtained. Under the same conditions, polysubstituted benzoic acids also performed well, affording the desired products in moderate to excellent yields. It is worth noting that when *ortho*-nitrobenzoic acid was applied, a secondary amide **3o** was unexpectedly observed. However, in the case that a nitro group is located in the *meta* or *para* position of the benzene ring in benzoic acid, tertiary amides **3m** and **3n** were found to be the main products, respectively. In view of the strong electron-withdrawing ability of the nitro group, we speculated that tertiary amides might be hydrolyzed into second amides when using substrates bearing a strong EWG in the benzene rings. In order to confirm our speculation, we chose 2-chloro-4-nitrobenzoic acid as the substrate. However, only product **3q** was isolated. Although it is insufficient to draw a conclusion on what would be the exact driving forces for the two possible products on the basis of these data, it is possible that both electronic and steric effects of substituted groups on the phenyl ring play a key role in the reactivity. In addition, it was noticed that for some substrates, such as 2-iodo-, 2-phenyl- and 4-phenylbenzoic acids, the yields of the desired products can be significantly improved by raising the ratio of AIBN to benzoic acid from 2:1 to 4:1. Aliphatic acids such as phenylacetic acid and acetic acid were also investigated, and no amide products could be detected after reaction. In addition, *para*-substituted hydroxybenzoic acid was investigated as the substrate and the desired product **3x** could not be detected.

Except for simple benzoic acids, two types of important conjugated carboxylic acids including cinnamic acids and phenylpropiolic acids were also found to

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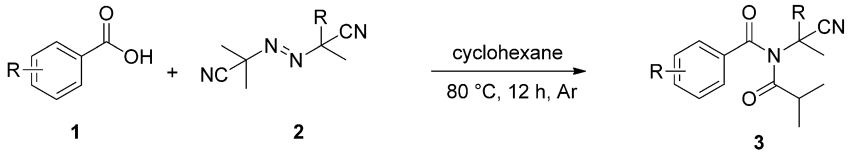
Table 2. Preparation of isobutyronitrile amides through the reaction between aromatic carboxylic acids and AIBN.[a]



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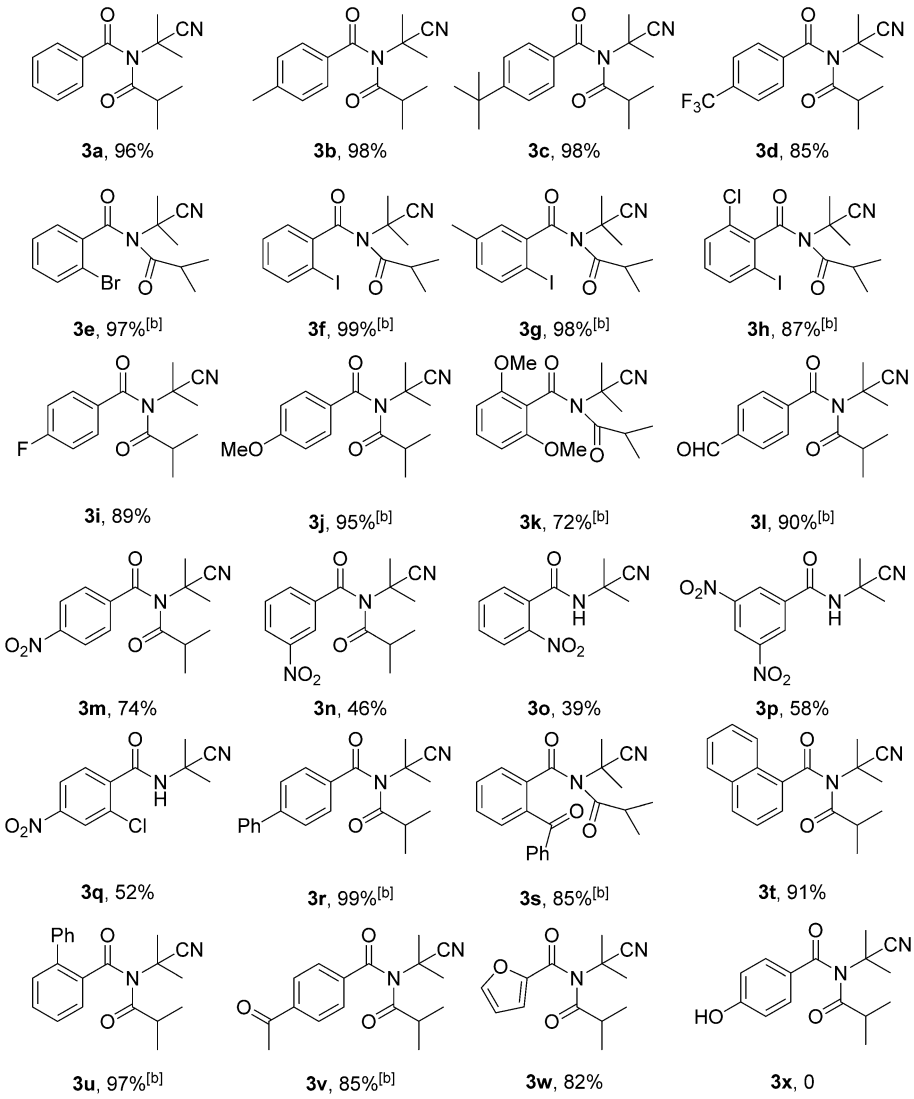

[a] *Reaction conditions:* benzoic acid (0.3 mmol), AIBN (0.6 mmol), cyclohexane (2 mL), 80 °C, 12 h, Ar, Isolated yield.
[b] AIBN (1.2 mmol).

be suitable substrates for the preparation of the corresponding isobutyronitrile amides. In these cases, the best results were obtained when using trichloroethane as a solvent under 110 °C. Some cinnamic acids and phenylpropiolic acids bearing different substituents were investigated under the optimized conditions and the corresponding products were isolated in moderate yields (Table 3). Notably, all of these products are secondary amides, and no tertiary amides were detected during the reaction, indicating that the tertiary amides might have been hydrolyzed into secondary amides once formed, as proposed above.

In order to gain further insights into the reaction mechanism, azo-*tert*-butane was used to replace AIBN for the reaction with benzoic acid under the same conditions. As expected, no reaction was observed and only the starting materials were recovered (Scheme 2), highlighting the essential role of AIBN for the desired transformation. Interestingly, one of the AIBN analogues, AMBN [2,2′-azodi(2-methylbu-

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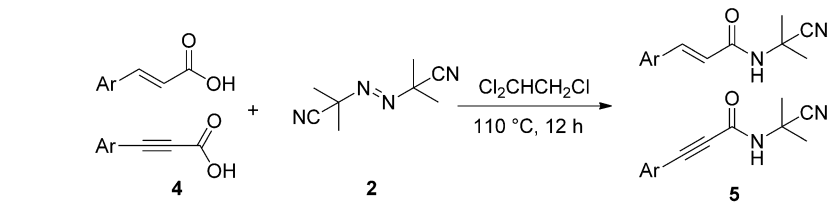
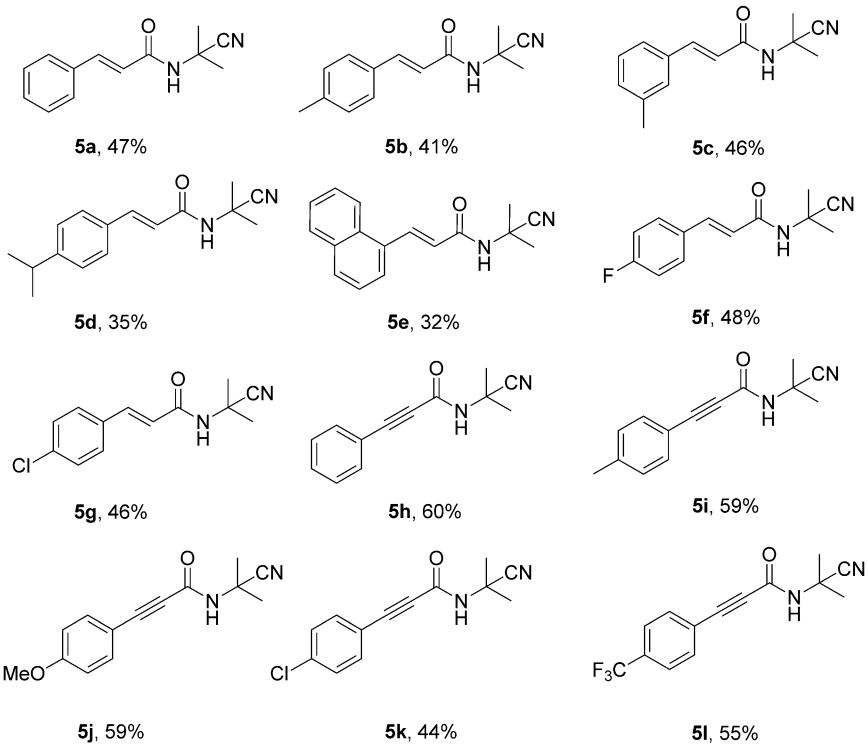
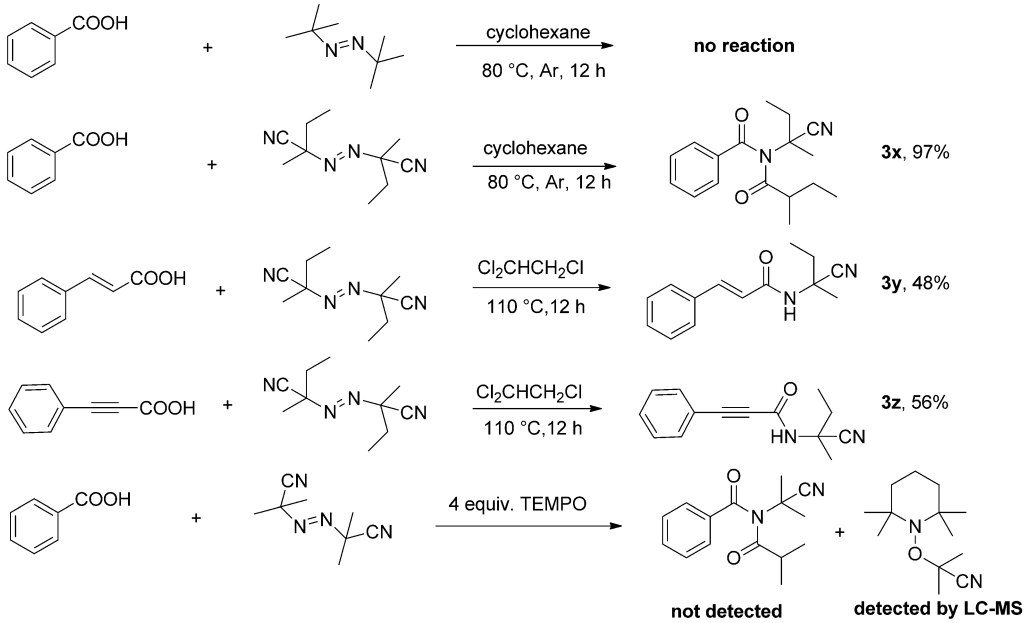
Table 3. Preparation of isobutyronitrile amides through the reaction between cinnamic or phenylpropiolic acids and AIBN.[a]





[a] *Reaction conditions:* carboxylic acid (0.3 mmol), AIBN (0.6 mmol), trichloroethane (2 mL), 110 °C, 12 h; isolated yields are indicated.



Scheme 2. Some control experiments to elucidate the mechanism.

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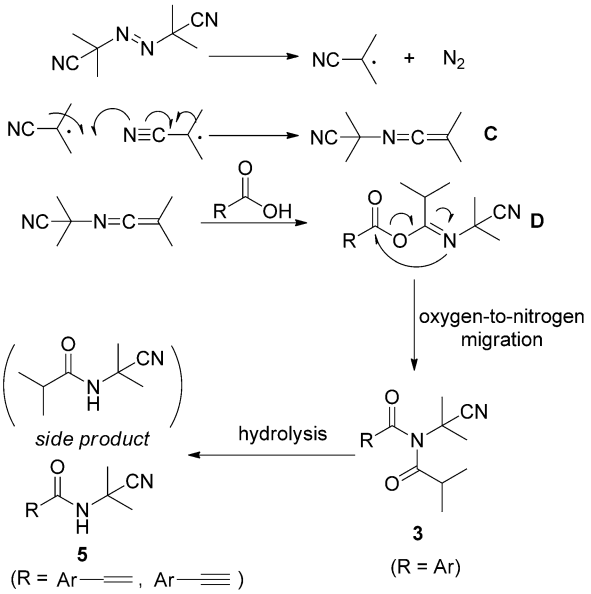

Scheme 3. Proposed mechanism for the formation of *N*-isobutyronitrile amide.

tyronitrile)] also reacted smoothly with benzoic acid to afford the product (**3x**) in 97% yield. Likewise, the reactions between cinnamic or phenylpropiolic acids and AMBN also gave the corresponding products (**3y** and **3z**) in 48% and 56% isolated yields. Finally, the reaction was completely inhibited by TEMPO under the standard conditions (Scheme 2), suggesting that the reaction was likely to occur through a radical process.

Based on the results described above as well as those found in the literature,[7,8] we propose a plausible mechanism as exhibited in Scheme 3. Firstly, an isobutyronitrile radical is released from AIBN by heating, which then reacts with another radical to generate **C**.[7] Subsequently, benzoic acid undergoes addition to the carbon-carbon double bond of **C** to form intermediate **D**.[8] Then, intermediate **D** rearranges to give the product by an oxygen-to-nitrogen migration of the alkoxycarbonyl group.[8] In cases that the carboxylic acids were alkynylcarboxylic acids or cinnamic acids, secondary amine product **3** would be formed *via* a hydrolysis process, and thus the isopropionyl group could be removed. Indeed, the proposed hydrolysis process is supported by the fact that a similar side product, *N*-(2-cyanopropan-2-yl)isobutyramide was detected by LC-MS from the reaction mixture, as was another species, cinnamic acid anhydride, which is also a possible by-product resulting from the hydrolysis process. This is also in consistence with the fact that only moderate yields of desired products **5** were isolated as listed in Table 3.

In conclusion, we reported an effective one-step pathway to prepare isobutyronitrile amides through the reaction between carboxylic acids and AIBN. These reactions were carried out smoothly under catalyst-free conditions, and both tertiary and secondary isobutyronitrile amide products are obtained in moderate to high yields, depending on the given carboxylic acids. The methodology as disclosed here features simple operating, environmentally friendly, highly efficient and excellent substrate tolerance, providing a practical way to the synthesis of a class of isobutyronitrile amide compounds that are remarkably valuable in the development of novel chemical and biological pharmaceuticals.

Experimental Section

General Experimental Methods

All reactions were carried out under air. Solvents were dried and degassed by standard methods. All of the benzyl halides and carboxylic acids are readily available. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were measured in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 MHz or 300 MHz) with TMS as an internal reference. Products were characterized by comparison of their ^{1}H NMR, ^{13}C NMR and TOF-MS data with those in the literature.

General Procedure for the Reaction between Aromatic Carboxylic Acids and AIBN

To a Schlenk tube equipped with a magnetic stir bar was added under argon, benzoic acid (0.3 mmol) and AIBN (0.6 mmol). Under argon, cyclohexane (2.0 mL) was then added. The resulting reaction mixture was kept stirring at 80 °C for 12 h. At the end of the reaction, the reaction mixture was cooled to room temperature. After removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether mixtures to afford the desired product in high purity.

General Procedure for the Reaction between Cinnamic or Phenylpropiolic Acids and AIBN

To a Schlenk tube equipped with a magnetic stir bar was added cinnamic acid or phenylpropiolic aicd (0.3 mmol), AIBN (0.6 mmol) and trichloroethane (2.0 mL). The resulting reaction mixture was kept stirring at 110 °C for 12 h. At the end of the reaction, the reaction mixture was cooled to room temperature. After removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether mixtures to afford the desired product in high purity.

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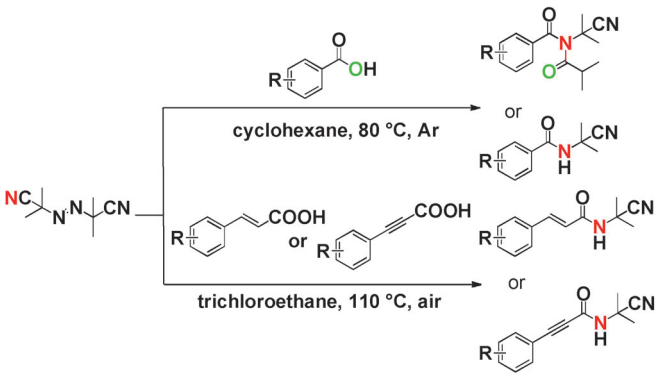

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