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Development of a Process for Triazine-Promoted Amidation of Carboxylic Acids

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Abstract:

A process has been developed for the triazine-promoted amidation of carboxylic acids. We have identified 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) as a cost-effective reagent for this transformation. The procedure is a suitable alternative to traditional amidation processes when an acid chloride cannot be prepared from the corresponding carboxylic acid due to safety, stability, or handling concerns.

Introduction

Amides are typically prepared by coupling an amine with an acid chloride generated from the parent carboxylic acid. While acid chlorides are highly reactive reagents, they suffer from several disadvantages. When an acid chloride is not commercially available, its manufacture can present handling and safety concerns. Though technically simple, conversion of a carboxylic acid to the corresponding acid chloride can be cumbersome in a plant. The acid chloride is often generated from an acid derivative such as an ester as part of a multistep synthesis; in this case, the carboxylic acid intermediate must be filtered and dried or extracted into a suitable solvent and dried azeotropically. These steps add cost through increased cycle times.

The typical reagents employed to prepare an acid chloride from a carboxylic acid are corrosive (thionyl chloride) or toxic (phosgene). While these reagents are inexpensive and very useful in the preparation of many acid chlorides, there are some situations in which these reagents are unsuitable. Certain carboxylic acids, such as some optically active compounds, are unstable to acidic conditions. Additionally, some smaller manufacturing facilities such as pilot plants may not have the facilities or the desire to handle toxic or highly corrosive reagents. Acid chlorides also present handling and storage issues due to their corrosivity and water reactivity.

Acid anhydrides have been utilized as alternatives to acid chlorides in amidation procedures. However, this procedure is often problematic. If the carboxylic acid is converted to a symmetric anhydride, 1 equiv of carboxylic acid is lost as the byproduct of the amidation reaction. While expensive acids may be isolated and reconverted to anhydride, the additional processing required may be costly. If the acid is sufficiently expensive, a mixed anhydride may be prepared from an inexpensive material such as acetic acid. However, it is unlikely that only one of the acid components will couple with the amine, and a mixture of amide products is often obtained.

Because of the disadvantages associated with the use of acid chlorides and anhydrides in amidation reactions, amidation of carboxylic acids is an active area of research. A common approach involves treatment of the acid with a reagent to form an activated intermediate, which is then treated with an amine in situ to form the amide product. This approach is primarily of interest for the preparation of peptides. Many reagents have been identified that allow coupling of carboxylic acids and amines. However, most are quite expensive, and separation of the byproducts produced is difficult.

We have developed a process suitable for large-scale preparation of amides using carboxylic acids and a triazine reagent as the promoter. While our interest is in the preparation of amides which have activity as agrochemicals, the work may have peptide synthesis applications as well.

Results and Discussion

Very few reagents reported to promote amidation of carboxylic acids are suitable for adaptation to large-scale manufacture. Many of the known reagents are costly, particularly those developed for the synthesis of peptides. Additionally, separation of the byproduct produced from the activating reagent is difficult unless chromatographic techniques are employed. The most economically viable reagent disclosed in the literature is 2-chloro-4,6-dimethoxy-1,3,5-triazine.[1] The reagent is commercially available and is readily prepared from commercially available 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) using methanol and aqueous base.[2] When treated with equimolar amounts of a carboxylic acid and a tertiary amine base, the activated species shown in Scheme 1 is formed.[3] This intermediate reacts with an amine to form the amide and an insoluble hydroxytriazine byproduct, which is readily removed by filtration.

Our investigation began with an evaluation of the reaction conditions reported in the literature for amide formation using 2-chloro-4,6-dimethoxy-1,3,5-triazine. A carboxylic acid of interest, 3,5-dichloro-4-methylbenzoic acid, was combined with the triazine reagent and *N*-methylmorpholine at ambient temperature. The intermediate was treated with several amines, affording the desired amides cleanly and in good yield (Table 1).

Once the dimethoxytriazine reagent was proven to be an effective amidation promoter, we set out to improve upon

(1) (a) Kaminski, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901. (b) Kaminski, Z. J. *Synthesis* **1987**, 917. (c) Taylor, E. C.; Schrader, T. H.; Walensky, L. D. *Tetrahedron* **1992**, *48*, 19.

(2) (a) Menicagli, R.; Malanga, C.; Peluso, P. *Synth. Commun.* **1994**, *24*, 2153 and references therein. (b) Cronin, J. S.; Ginah, F. O.; Murray, A. R.; Copp, J. D. *Synth. Commun.* **1996**, *26*, 3491.

(3) Kaminski, Z. J.; Paneth, P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248.

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Scheme 1. **General scheme for amidation of carboxylic acids with dimethoxytriazine reagent**

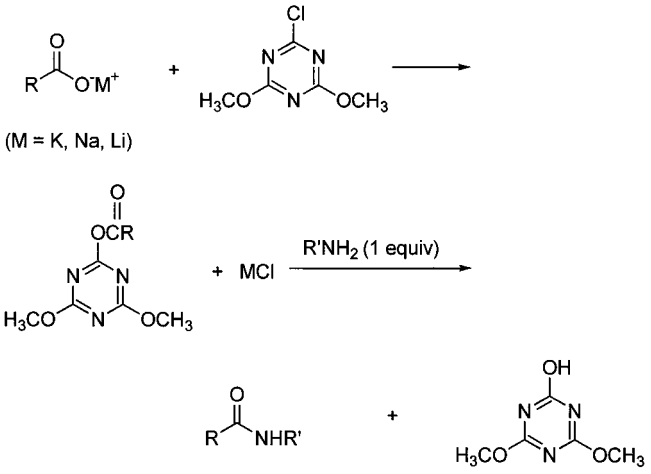


Table 1. **Amidation of 3,5-dichloro-4-methylbenzoic acid promoted by 2-chloro-4,6-dimethoxy-1,3,5-triazine**

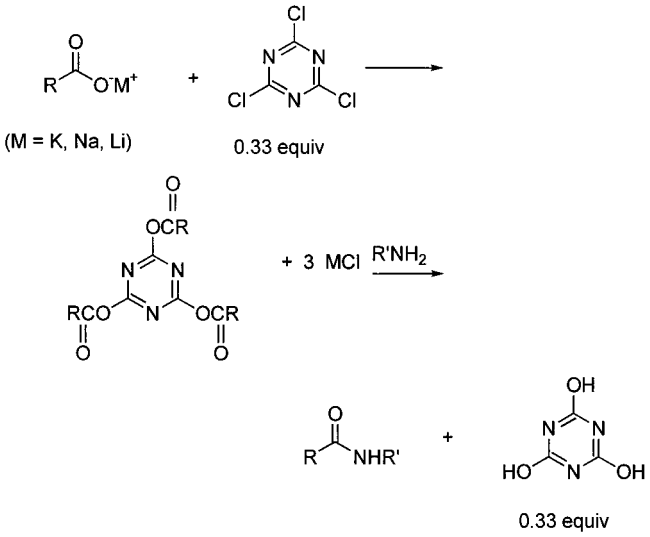
amine	product	time (h)	yield (%)
tert-octylamine	**1**	1	72
3-amino-1-chloro-3-methylpentan-2-one	**2**	6	68
3-amino-3-ethylpentyne	**3**	1	73

the reported reaction conditions to develop a process suitable for large-scale synthesis. First, we examined the utility of cyanuric chloride, the commercially available parent compound of the dimethoxytriazine reagent, as an amidation promoter. We theorized that use of the trichlorotriazine promoter would permit the use of only 0.33−0.5 mol of triazine reagent per mole of carboxylic acid employed. We found several references to the use of cyanuric chloride for amidation,[4] but the procedures were not well suited to scale-up. The triazine reagent and carboxylic acid were typically employed in a 1:1 ratio, which circumvents the advantage of employing the trichlorotriazine reagent. In each case, tertiary amine bases were used to generate the activated intermediate. These conditions were undesirable from cost and waste generation considerations.

We also found that there was some disagreement in the literature regarding the product of the reaction between cyanuric chloride and a carboxylic acid. It has been proposed that the product of this reaction is the corresponding acid chloride. If this were the case, this amidation procedure would be undesirable for racemizable substrates such as amino acids due to the presence of the hydrogen chloride byproduct. However, in our hands, no acid chloride was observed after the activation step. We successfully performed the amidation using 0.33 equiv of cyanuric chloride per mole of carboxylic acid. The experimental procedure was otherwise similar to that employed when using the dimethoxytriazine derivative. Based on these results, our proposed intermediate is the triacylated triazine shown in Scheme 2.

(4) (a) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037. (b) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227 and references therein. (c) Sainsbury, M.; Strange, R. H.; Woodward, P. R.; Barsanti, P. A. *Tetrahedron* **1993**, *49*, 2065. (d) Hinz, W.; Just, G. *Can. J. Chem.* **1987**, *65*, 1503.

Scheme 2. **General scheme for amidation of carboxylic acids with cyanuric chloride**



The nature of the base used to generate the carboxylate salt was not critical. While tertiary amine bases were effective, we preferred to develop a procedure employing an inorganic base. Aqueous sodium hydroxide was suitable, and the presence of water did not adversely affect intermediate formation. It should be noted that the sodium hydroxide was depleted by adding the carboxylic acid before the triazine reagent in order to avoid hydroxytriazine formation. The intermediate formed rapidly, as evidenced by precipitate formation and heat evolution upon addition of the triazine to the carboxylate salt. We also utilized preformed carboxylate salts in the reaction, demonstrating that base is not required for this procedure. This modification is useful when the desired substrate is a commercially available carboxylate salt or when it is necessary to isolate the salt due to purification or other handling considerations. Upon addition of a primary amine, a second exotherm was observed; amidation was typically complete within 1 h. A summary of the experimental data appears in Table 2.

The cyanuric chloride-promoted process has several advantages that make it suitable for large-scale manufacture of amides. The ability to use only 0.33 equiv of the triazine promoter is advantageous because it minimizes reagent utilization and byproduct generation compared to the dimethoxytriazine procedure. The reaction is robust, as the presence of water in both the activation and amidation steps is tolerated. This is an important feature for two reasons. First, inexpensive inorganic bases may be used to generate the carboxylate anion required in the activation step. This improvement simplifies the byproduct streams; we have eliminated the amine bases used in the literature which would have to be disposed of or recycled. The water tolerance of the procedure is also desirable because some amines of interest are isolated as solutions in solvent−water azeotropes. Another advantage of the process is that separation of the byproduct is simple. The precipitated cyanuric acid is readily separated by filtration, while the amide product remains in

Table 2. **Cyanuric chloride-promoted amidation of carboxylic acids**

carboxylic acid/base	amine	product	time (h)	yield (%)
3,5-dichlorobenzoic acid, *N*-methylmorpholine (NMM)	3-amino-3-methylbutyne (aqueous solution)	**4**	1	69
propionic acid, NMM	3,4-dichloroaniline	**5**	1	73
3,5-dichloro-4-methylbenzoic acid, NMM	3-amino-3-methylpentyne (aqueous solution)	**6**	2	72
3,5-dichloro-4-methylbenzoic acid, NaOH	3-amino-3-methylpentyne (aqueous solution)	**6**	0.5	75
potassium benzoate, no added base	*tert*-octylamine	**7**	1	65
potassium benzoate, no added base	3-amino-3-methylpentyne (aqueous solution)	**8**	0.5	44

solution. Residual cyanuric acid can be removed with a base wash. Another attractive feature of this process is that amidation occurs readily, even when sterically hindered primary *tert*-alkylamines are employed in the reaction.

While the yields achieved to date are acceptable (typically 65−75%), they do not currently match yields obtained from traditional amidation methods. Occasionally, unreacted carboxylic acid is observed in the reaction mixture and removed with a base wash. No side products are observed in most cases, indicating that yield losses occur during workup. We believe that the losses are occurring during filtration, when product is trapped with the cyanuric acid byproduct. These losses can be minimized by effective deliquoring and washing during solid−liquid separation of the byproduct and the solution containing the amide product.

Conclusions

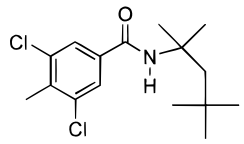
The amidation of carboxylic acids promoted by triazine reagents is an alternative to traditional amidation procedures employing acid chlorides. We have developed a process for this transformation which utilizes 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) as the activating agent. The ability to avoid the preparation and handling of acid chlorides and the ease of byproduct separation are key features of this chemistry.

Experimental Section

General Information. Solvents and reagents were obtained from commercial sources and used without purification unless otherwise indicated. Gas chromatography was performed using a Hewlett-Packard 5890A chromatograph equipped with a flame ionization detector. ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, using tetramethylsilane as an internal standard. Melting points are uncorrected.

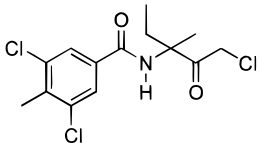
General Procedure for 2-Chloro-4,6-dimethoxy-1,3,5-triazine-Promoted Amidation of 3,5-Dichloro-4-methylbenzoic Acid. A slurry of 3,5-dichloro-4-methylbenzoic acid (2.0 g, 9.75 mmol) in a polar organic solvent was treated with 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.71 g, 9.75 mmol) and *N*-methylmorpholine (1.01 g, 9.94 mmol). A slight exotherm (1−2 °C) was observed, and most of the solids dissolved. The reaction mixture thickened noticeably after 20−40 min. After the mixture was stirred for 1 h at ambient temperature, the amine reagent (1.02−1.05 equiv) was added, and a second exotherm of 2−4 °C occurred. The reaction was stirred at the temperature noted and was judged to be complete by GC analysis of the reaction mixture. The slurry was cooled to room temperature and filtered. The solid was washed with a minimal amount of solvent; the filtrates were combined and washed with 1 M sodium hydroxide solution and with water. The organic layer was dried over sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was dried under vacuum to yield the amide product.

3,5-Dichloro-4-methyl-*N*-(1,1,3,3-tetramethylbutyl)-benzamide (1). Following the general procedure, a slurry of the carboxylic acid in acetonitrile (20 mL) was treated with the triazine reagent and amine base. The resulting slurry was treated with *tert*-octylamine (1.32 g, 10.24 mmol) at ambient temperature for 1 h. Workup as described above afforded the amide as a white solid (2.21 g, 72%): mp 150−152 °C; ^{1}H NMR (DMSO-d_6) δ 7.85 (s, 2H), 2.44 (s, 3H), 1.84 (s, 2H), 1.41 (s, 6H), 0.95 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 163.1, 136.0, 135.6, 134.3 (2C), 126.6 (2C), 54.8, 49.2, 31.3, 31.0, 29.4, 17.2; MS (CI) *m*/*z* 316 (M + H). Anal. Calcd for $C_{16}H_{23}Cl_2NO$: C, 60.76; H, 7.33; N, 4.43; Cl, 22.42. Found: C, 60.82; H, 7.12; N, 4.38; Cl, 22.21.



1

3,5-Dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide (2).[5] Following the general procedure, a slurry of the carboxylic acid in *tert*-butyl methyl ether (35 mL) was treated with the triazine reagent and amine base. Addition of 3-amino-1-chloro-3-methylpentan-2-one hydrochloride[6] (1.85 g, 9.94 mmol) and *N*-methylmorpholine (3.5 mL) afforded a slurry, which was stirred for 6 h at 55 °C. Workup yielded the amide (2.24 g, 68%) as a white solid: mp 158−160 °C (lit.[7] mp 157−158 °C).



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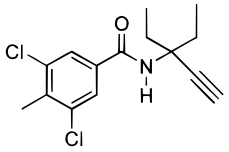
3,5-Dichloro-*N*-(1,1-diethyl-2-propynyl)-4-methylbenzamide (3). Following the general procedure, a slurry of the

(5) Michelotti, E. L.; Young, D. H. U.S. Patent 5304572, 1994.
(6) Michelotti, E. L.; Rayle, H. L.; Stephens, R. W.; Zabrodski, W. J. U.S. Patent 5874466, 1999.
(7) Rayle, H. L.; Roemmele, R. C.; Stephens, R. W. U.S. Patent 5859254, 1999.

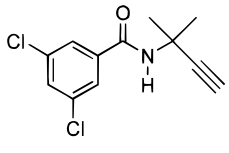
carboxylic acid in *tert*-butyl methyl ether (35 mL) was treated with the triazine reagent and amine base. The resulting slurry was treated with 3-amino-3-ethylpentyne (1.11 g, 9.94 mmol) and stirred at 55 °C for 1 h. Workup afforded the amide as a white solid (2.12 g, 73%): mp 122−124 °C; ^{1}H NMR (DMSO-d_6) δ 8.21 (bs, 1H), 7.89 (s, 2H), 3.24 (s, 1H), 2.44 (s, 3H), 1.98 (dq, 4H, J = Hz), 0.94 (t, 3H, J = Hz); ^{13}C NMR (DMSO-d_6) δ 163.0, 136.4, 134.5, 134.3 (2C), 126.9 (2C), 85.2, 73.6, 55.8, 29.7 (2C), 17.2, 8.4 (2C); MS (CI) m/z 298 (M + H). Anal. Calcd for $C_{15}H_{17}Cl_2NO$: C, 60.41; H, 5.75; N, 4.70; Cl, 23.78. Found: C, 60.28; H, 5.41; N, 4.63; Cl, 23.66.



3

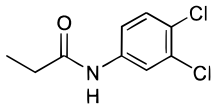
General Procedure for 2,4,6-Trichloro-1,3,5-triazine-Promoted Amidation Using *N*-Methylmorpholine as Base. A slurry of the carboxylic acid (1 equiv) in a polar organic solvent was treated with 2,4,6-trichloro-1,3,5-triazine (0.33 equiv) and *N*-methylmorpholine (1.02 equiv). A 12−13 °C exotherm was observed, and a precipitate formed upon addition of the amine base. After the slurry was stirred for 1 h, the primary amine (1.02−1.05 equiv) was added; a 3−5 °C exotherm was observed. The reaction was judged to be complete by GC analysis. The slurry was cooled to room temperature and filtered. The solid was washed with a minimal amount of solvent. The filtrates were combined and washed with 1 M sodium hydroxide solution and with water. The organic layer was dried over sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was dried under vacuum to yield the amide product.

3,5-Dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide (4).[8] Following the general procedure, a slurry of 3,5-dichlorobenzoic acid (2.0 g, 10.47 mmol) in *n*-butyl acetate (35 mL) was treated with 2,4,6-trichloro-1,3,5-triazine (0.64 g, 3.49 mmol) and *N*-methylmorpholine (1.08 g, 10.68 mmol). The resulting slurry was treated with 3-amino-3-methylbutyne (0.99 g of a 90% solution in water, 10.68 mmol) and stirred at 23 °C for 1 h. Workup as described above afforded the amide as a white solid (1.86 g, 69%): mp 154−156 °C (lit.[9] mp 155−157 °C). The spectral data obtained were identical with those of an authentic sample.



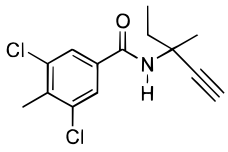
4

N-(3,4-Dichlorophenyl)propionamide (5).[10] Following the general procedure, a solution of propionic acid (10.0 g, 134.99 mmol) in *n*-butyl acetate (100 mL) was treated with 2,4,6-trichloro-1,3,5-triazine (8.30 g, 44.99 mmol) and *N*-methylmorpholine (13.93 g, 137.7 mmol). The resulting slurry was treated with 3,4-dichloroaniline (22.31 g, 137.7 mmol), and the reaction mixture was stirred at 23 °C for 1 h. Workup afforded the amide as a pale tan solid (21.54 g, 73%): mp 86−88 °C (lit.[11] mp 86−91 °C). The spectral data obtained were identical with those of an authentic sample.



5

3,5-Dichloro-*N*-(1-ethyl-1-methyl-2-propynyl)-4-methylbenzamide (6). Following the general procedure, a slurry of 3,5-dichloro-4-methylbenzoic acid (2.5 g, 12.19 mmol) in *n*-butyl acetate (40 mL) was treated with 2,4,6-trichloro-1,3,5-triazine (0.74 g, 4.02 mmol) and *N*-methylmorpholine (1.26 g, 12.43 mL). The resulting slurry was treated with 3-amino-3-methylpentyne (1.63 g of a 74% solution in water, 12.43 mmol) and stirred at 23 °C for 2 h. Workup gave the amide as a white solid (2.50 g, 72%): mp 119−120 °C; ^{1}H NMR (DMSO-d_6) δ 8.32 (bs, 1H), 7.89 (s, 2H), 3.18 (s, 1H), 2.44 (s, 3H), 1.95 (dq, 2H, J = Hz), 1.56 (s, 3H), 0.95 (t, 3H, J = Hz); ^{13}C NMR (DMSO-d_6) δ 162.9, 136.5, 134.4, 134.4 (2C), 126.8 (2C), 86.4, 72.4, 51.1, 32.5, 26.0, 17.2, 8.5; MS (CI) m/z 284 (M + H). Anal. Calcd for $C_{14}H_{15}Cl_2NO$: C, 59.17; H, 5.32; N, 4.93; Cl, 24.95. Found: C, 59.02; H, 5.09; N, 4.97; Cl, 25.02.

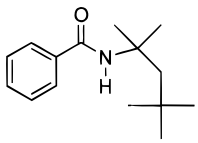


6

3,5-Dichloro-*N*-(1-ethyl-1-methyl-2-propynyl)-4-methylbenzamide (6): Carboxylate Formation Using Aqueous Inorganic Base. Sodium hydroxide (9.75 mL of a 1 M solution, 9.75 mmol) was added to a slurry of 3,5-dichloro-4-methylbenzoic acid (2.0 g, 9.75 mmol) in acetonitrile (40 mL). A 4 °C endotherm was observed. The reaction mixture was stirred for 2 h, and then 2,4,6-trichloro-1,3,5-triazine (0.59 g, 3.22 mmol) was added. The resulting slurry was stirred for 2 h and treated with 3-amino-3-methylpentyne (1.34 g of a 74% solution in water, 10.24 mmol); a 3 °C exotherm was observed. The reaction was stirred at 23 °C for 2 h and worked up as described in the general procedure to give the amide as a white solid (2.09 g, 75%). The spectral data obtained matched those listed above.

(8) Propyzamide, manufactured and marketed as Kerb herbicide by Rohm and Haas Co., Philadelphia, PA.
(9) Swithenbank, C.; McNulty, P. J.; Viste, K. L. *J. Agric. Food Chem.* **1971**, *19*, 417.
(10) Propanil, manufactured and marketed as Stam herbicide by Rohm and Haas Co., Philadelphia, PA.
(11) Schaefer, W.; Wegler, R. French Patent FR 1339155, 1963; *Chem. Abstr.* **1964**, *60*, 2861a.

***N*-(1,1,3,3-Tetramethylbutyl)benzamide (7):**[12] **Amidation Using Carboxylate Salt without Added Base.** A slurry of potassium benzoate (2.0 g, 12.48 mmol) in 40 mL of 7:1 acetonitrile−water was treated with 2,4,6-trichloro-1,3,5-triazine (0.76 g, 4.12 mmol). The mixture was stirred for 1 h, and *tert*-octylamine (1.69 g, 13.10 mmol) was added. A 4 °C exotherm was observed. The reaction was stirred at 23 °C for 1 h. Workup as described in the general procedure afforded the amide as a white solid (1.92 g, 65%): mp 63−65 °C (lit.[13] mp 67−69 °C).



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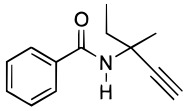
(12) (a) Lacey, R. N. *J. Chem. Soc.* **1960**, 1633. (b) Alender, J.; Morgan, P.; Timberlake, J. *J. Org. Chem.* **1983**, *48*, 755.
(13) Johnson, R. A.; Murray, H. C.; Reineke, L. M. *J. Am. Chem. Soc.* **1971**, *93*, 4872.

***N*-(1-Ethyl-1-methyl-2-propynyl)benzamide (8):**[14] **Amidation Using Carboxylate Salt without Added Base.** A slurry of potassium benzoate (2.0 g, 12.48 mmol) in 35 mL of 4:1 acetonitrile−water was treated with 2,4,6-trichloro-1,3,5-triazine (0.76 g, 4.12 mmol). A 2 °C exotherm was observed. The mixture was stirred for 1 h, and 3-amino-3-methylpentyne (1.72 g of a 74% solution, 13.10 mmol) was added. The reaction was stirred at 23 °C for 0.5 h. Workup as described in the general procedure afforded the amide as a white solid (1.08 g, 44%): mp 105−107 °C (lit.[14] mp 106−107 °C).



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(14) Hennion, G. F.; Teach, E. G. *J. Am. Chem. Soc.* **1953**, *75*, 1653.