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A facile and efficient synthesis of 2,2,2-trifluoroethyl 2-[(*E*)-*N*-phenylcinnamamido]-2-phenylacetates in trifluoroethanol via sequential Ugi four-component reaction/esterification

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Dedicated to Professor Majid M. Heravi on the occasion of his 60th birthday

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ABSTRACT

We describe an efficient approach for the synthesis of N-substituted 2-alkenylamides in trifluoroethanol via an Ugi 4-component reaction in short reaction times. The use of a catalytic amount of sulfuric acid in trifluoroethanol gave the desired trifluoroethyl derivatives in good to high yields.

Multicomponent reactions (MCRs) have attracted considerable interest owing to their exceptional synthetic efficiency.[1,2] MCRs have a high attendant bond forming efficiency and easily install molecular complexity and diversity.[3] The wide variation in starting materials available for MCRs opens up versatile opportunities for the synthesis of compound libraries. Reactions that result in the formation of carbon–carbon, carbon–nitrogen, and other carbon–heteroatom bonds at the same time, and that introduce heteroatom-containing functionality into structural frameworks are especially attractive for the rapid construction of organic molecules.[4]

Isocyanide-based MCRs (IMCRs) allow the synthesis of a large number of different scaffolds. The significant potential of isocyanides for the development of multicomponent reactions is a result of their ability to take part in diverse bond formation processes, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed.[5] Therefore, the design of novel IMCRs, has attracted attention in areas such as drug discovery, organic synthesis, combinatorial chemistry, and materials science.[6]

Highly fluorinated alcohols exhibit very good hydrogen bonding donor ability, low nucleophilicity, high ionizing power, and ability for hydrogen bonding with water. Reactions in fluorinated alcohols are generally selective and do not result in by-product formation. Also, isolation of the products is simple and fluorinated alcohols can be easily recovered by distillation.[7]

Among several fluorinated alcohols, the most commonly used and the cheapest are trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP).[8] Due to their activity, these solvents have been used for various reactions, such as the activation of orthoesters,[9] synthesis of heterocycles,[10] and condensation reactions.[11]

The Ugi 4-component reaction (Ugi-4CR) is one of the cornerstones of multicomponent processes, and many efforts have been devoted to the exploration of the potential of this transformation.[12]

According to the literature, pseudopeptides have been prepared via the Ugi-4CR of an appropriate primary amine, carbaldehyde, isocyanide, and carboxylic acid derivative in an organic solvent. This reaction normally takes about 24 h, and in some cases with substituted amines or carboxylic acids up to seven days. Hence, there is a strong demand for a highly efficient and environmentally benign method to prepare functionalized pseudopeptides. In

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continuation of our interest in multicomponent reactions, we report the Ugi-4CR in trifluoroethanol for the synthesis of novel N-substituted alkenylamides **5a**–**g** and sequential trifluoroethyl esterification in trifluoroethanol to afford 2,2,2-trifluoroethyl esters **6a**–**g** using catalytic sulfuric acid. Initially, the four-component reaction of benzaldehyde **1**, primary amines **2**, unsaturated carboxylic acids **3**, and isocyanide **4**, in TFE at room temperature leads to N-substituted alkenylamides **5** (Scheme 1). The products **5** could be converted into the trifluoroethyl esters **6** in the presence of a catalytic amount of sulfuric acid (Scheme 1).

2,2,2-Trifluoroethanol exhibits high ionization ability and can promote reactions with polar intermediates.[13–15] It is well known that the Ugi-4CR involves an initial condensation between a primary amine and a carbonyl compound to form an imine, followed by protonation of the imine by a carboxylic acid. The resulting iminium ion reacts with the isocyanide and the carboxylate. It is clear that formation of the intermediate iminium ion could be accelerated in trifluoroethanol. To examine this idea, the four-component reaction of benzaldehyde, aniline, cinnamic acid, and *t*-butyl isocyanide was selected as a model system. The reaction was studied in methanol as the usual solvent for the Ugi-4CR and also in TFE. TLC analysis showed that the reaction in TFE was complete after 11 h, while 24 h were required in methanol. The yield of the **5a** was 75% in MeOH and 85% in TFE. The spectroscopic data of product **5a** were identical to those of an authentic sample. In another reaction, the Ugi product was not isolated and two drops of concentrated sulfuric acid were added to the mixture. Following work-up, spectroscopic data revealed that the product was trifluoroethyl ester **6a**. We assume that the expected Ugi product **5a**, initially formed under the reaction conditions, subsequently undergoes spontaneous irreversible amide acidic esterification to form the trifluoroethyl ester **6a** (Scheme 2).

To investigate the effect of acid on this reaction, different Brønsted acids such as methanesulfonic acid, trifluoroacetic acid (TFA), silica sulfuric acid (SSA), and the Lewis acids cuprous iodide and zinc chloride were used. In the case of methanesulfonic acid, a mixture of products was obtained, and in the other cases, trifluoroethyl ester **6a** was not formed. The results are summarized in Table 1.

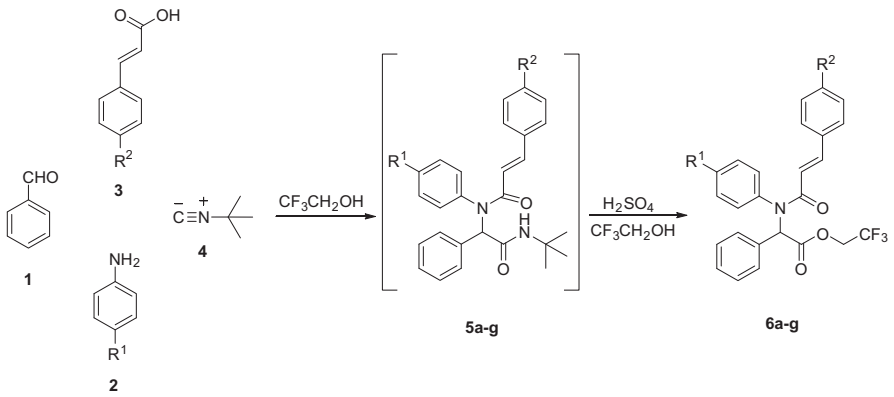
When cuprous iodide or zinc chloride was used, the obtained products were separated and identified as α-amino amide **7** and unsaturated ester **8** (Scheme 3).

It would appear that the formation of a complex with the metal increases the electrophilicity of the α,β-unsaturated amide group and enhances nucleophilic acyl substitution by TFE (Scheme 4).

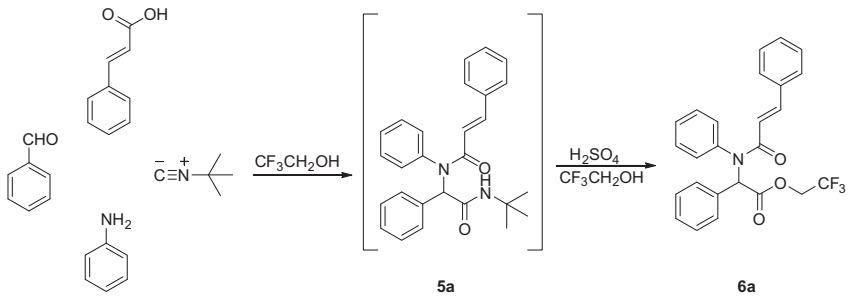
These results encouraged us to explore the optimized reaction conditions with different carboxylic acids and primary amines. The results are summarized in Table 2.

The structures of the products **6a**–**g** were characterized using spectroscopic data. In **6b** there was a doublet of quartets for the CH_2–CF_3 and a signal in the region δ 6.15–6.30 due to the –C(sp^3)–H hydrogen atom, but in some cases methylene was observed as a multiplet. The *E*-configuration of the double bond was identified by the magnitude of the coupling constant between the two alkene protons (ca. 15.5 Hz). The atypical chemical shift for the alkene protons is due to the conjugation of double bond with the adjacent carbonyl moiety. A notable signal in ^{13}C NMR spectra of the products is that of the –OCH_2 group which occurs as a quartet at δ 60.9 as a result of the coupling with the trifluoromethyl moiety. The carbonyl group resonances in the ^{13}C NMR spectra of compound **6a** appeared at δ 166.6–169.1 ppm. The mass spectra of these compounds displayed molecular ion peaks at the expected *m*/*z* values.

To investigate in more detail this sequential Ugi/esterification method, we performed the reaction in two separate steps. The first step was an Ugi-4CR between the aromatic aldehyde, aniline derivative, cinnamic acid, and *t*-butyl isocyanide to form the Ugi-pseudopeptides **5a**–**g**. Next, these products were hydrolyzed and



Scheme 1.

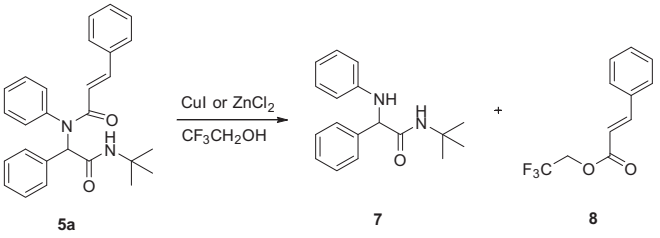


Scheme 2. Synthesis of 2,2,2-trifluoroethyl 2-[(*E*)-*N*-phenylcinnamamido]-2-phenylacetate **6a** as a model compound.

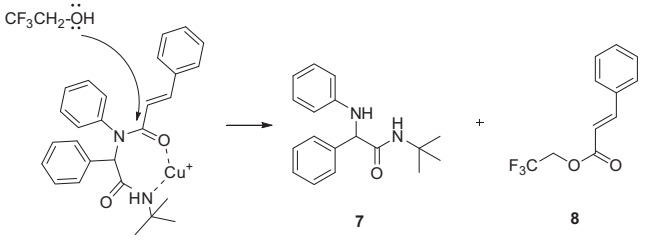
Table 1
Identification of suitable reaction conditions for the synthesis of compound **6a**

Catalyst	Temperature	Products	Yield (%)
CF_3SO_3H	rt	Several products	0
TFA	Reflux or rt	NR	0
SSA	Reflux or rt	NR	0
CuI	Reflux or rt	NR	0
$ZnCl_2$	Reflux or rt	NR	0
H_2SO_4	**rt**	**6a**	**55**

NR = no reaction.



Scheme 3.



Scheme 4. Formation of amino amide **7** in the presence of CuI or $ZnCl_2$.

esterified as a domino process to form esters **6a–g** in 50–60% yields. The proposed mechanism is shown in Scheme 5. It seems reasonable to propose that the high polarity via stabilization of the iminium salts and the hydrogen bonding interaction of TFE may be responsible for promoting the reaction.

In conclusion, we have described TFE as an efficient medium for the synthesis of N-substituted alkenylamides in good isolated yields. In contrast to the existing methods which require between 24 and 36 h for the completion of the Ugi reaction, the present method offers the following competitive advantages: (i) shorter reaction times, (ii) higher yields compared to the reported methods. The corresponding trifluoroethyl ester derivatives **6a–g** were formed via the addition of a catalytic amount of sulfuric acid to form the trifluoroethyl esters in good yields.

General procedure for the synthesis of 2,2,2-trifluoroethyl 2-[(*E*)-*N*-phenylcinnamamido]-2-phenylacetates 6a–g

Aniline derivative (1 mmol), aldehyde (1 mmol), and TFE (5 mL) were stirred for 30 min. Then, cinnamic acid (148 mg, 1 mmol) and, after 15 min, *t*-butyl isocyanide (83 mg, 1 mmol) were added and the mixture was stirred for 10–11 h. The progress of the reaction was monitored by TLC (eluent hexane/ethyl acetate 5:1). Sulfuric acid (98%, 2 drops) was added to the solution of Ugi adduct in TFE. The mixture was stirred at room temperature for 10 min. The progress of the reaction was monitored by TLC (eluent hexane/ethyl acetate 3:1).

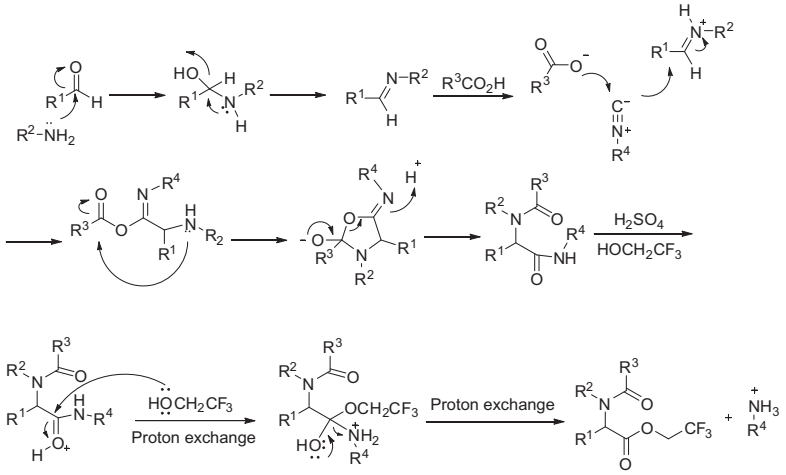
After this time, the reaction mixture was evaporated and after washing with H_2O was extracted with EtOAc. The combined organic layers were dried with sodium sulfate, and concentrated to dryness in vacuum. The final purification was done by silica gel column chromatography eluted by an EtOAc/hexane (1:3) mixture, to afford the corresponding pure **6a–g** with 50–60%.

Table 2
Synthesis of trifluoroethyl ester via sequential Ugi-4CR/esterification reactions

R^1	R^2	Product	R^1	R^2	Product
H	H	**6a** 55%, 11 h	Cl	H	**6e** 55%, 11 h
H	Cl	**6b** 52%, 12 h	Cl	Cl	**6f** 50%, 12 h
Br	Cl	**6c** 51%, 12 h	Et	H	**6g** 60%, 10 h
Br	H	**6d** 57%, 11 h			

Selected data for compounds 6a–g: 2,2,2-trifluoroethyl 2-[(*E*)-*N*-phenylcinnamamido]-2-phenylacetate (6a)

IR (NaCl, cm^{-1}): υ 1647, 1684, 3303; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.55–4.77 (m, 2H, OCH_2), 6.24 (s, 1H, CH), 6.26 (d, J = 15.4 Hz, 1H, C=CH), 7.14–7.33 (m, 15H, H-Ar), 7.79 (d, J = 15.5 Hz, 1H, C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 60.9 (q, J = 36.5 Hz, OCH_2), 64.0, 117.7, 120.9, 124.6, 128.0, 128.3, 128.6, 128.7, 128.9, 129.2, 130.0, 132.0, 132.5, 134.4, 134.7,



Scheme 5. Proposed mechanism for the sequential Ugi/trifluoroethyl esterification.

143.7, 166.6, 169.1; HR-MS (ESI) Calcd for $C_{25}H_{21}F_3NO_3$ $[M+1]^+$ 440.14678. Found 440.14680, Calcd for $C_{25}H_{20}F_3NNaO_3$ $[M+Na]^+$ 462.12875. Found 462.12875.

2,2,2-Trifluoroethyl 2-[(*E*)-3-(4-chlorophenyl]-*N*-phenylacrylamido)-2-phenylacetate (6b)

IR (NaCl, cm^{-1}): υ 1655, 1767.1654, 1767; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.49–4.74 (dq, 2H, J = 12.6, 8.4 Hz, OCH_2), 6.17 (d, J = 15.5 Hz, 1H, C=CH), 6.19 (s, 1H, CH), 7.08–7.26 (m, 14H, H-Ar), 7.69 (d, J = 15.5 Hz, 1H, C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 60.9 (q, J = 36.5 Hz, OCH_2), 64.5, 118.6, 120.9124.6, 128.4, 128.7, 128.9, 129.0, 129.1, 130.0, 130.4, 132.8, 133.4, 135.6, 138.9, 141.7, 166.4, 169.0; HR-MS (ESI) Calcd for $C_{25}H_{20}Cl\ F_3NO_3$ $[M+1]^+$ 474.10782. Found 474.10783, Calcd for $C_{25}H_{19}ClF_3NNaO_3$ $[M+Na]^+$ 496.08975. Found 496.08978.

2,2,2-Trifluoroethyl 2-[(*E*)-*N*-(4-chlorophenyl)cinnamamido]-2-phenylacetate (6e)

IR (NaCl, cm^{-1}): υ 1653, 1767; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.49–4.75 (m, 2H, OCH_2), 6.18 (d, J = 15.5 Hz, 1H, C=CH), 6.28 (s, 1H, CH), 7.06–7.31 (m, 13H, H-Ar), 7.76 (d, J = 15.5 Hz, 1H, C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 60.9 (q, J = 36.5 Hz, OCH_2), 64.0, 117.7, 120.9, 124.6, 128.0, 128.3, 128.6, 128.7, 128.9, 129.2, 130.0, 132.0, 132.5, 134.4, 134.7, 143.7, 166.6, 169.1; HR-MS (ESI) Calcd for $C_{25}H_{20}ClF_3NO_3$ $[M+1]^+$ 474.10778. Found 474.10783, Calcd for $C_{25}H_{19}ClF_3NNaO_3$ $[M+Na]^+$ 496.08975. Found 496.08978.

2,2,2-Trifluoroethyl 2-[(*E*)-*N*,3-bis(4-chlorophenyl)acrylamido]-2-phenylacetate (6f)

IR (NaCl, cm^{-1}): υ 1647, 1684, 3303; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.48–4.74 (m, 2H, OCH_2), 6.14 (d, J = 15.5 Hz, 1H, C=CH), 6.27 (s, 1H, CH), 7.04–7.28 (m, 13H, H-Ar), 7.69 (d, J = 15.5 Hz, 1H, C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 60.9 (q, J = 36.5 Hz, OCH_2), 65.0, 118.12, 120.9, 124.5, 127.9, 128.2, 128.5, 128.7, 129.0, 129.0, 129.2, 129.2, 130.0, 131.5, 131.9, 132.4, 133.1, 134.5, 135.9, 137.2, 142.3, 166.3, 169.1; HR-MS (ESI) Calcd for $C_{25}H_{19}Cl_2F_3NO_3$ $[M+1]^+$ 508.06883. Found 508.06886, Calcd for $C_{25}H_{18}Cl_2F_3NNaO_3$ $[M+Na]^+$ 530.05077. Found 530.05080.

2,2,2-Trifluoroethyl 2-[(*E*)-*N*-(4-ethylphenyl)cinnamamido]-2-phenylacetate (6g)

IR (KBr, cm^{-1}): υ 1655, 1767; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.50–4.74 (m, 2H, OCH_2), 6.16 (s, 1H, CH), 6.26 (d, J = 15.6 Hz, 1H, C=CH), 7.06–7.32 (m, 13H, H-Ar), 7.75 (d, J = 15.6 Hz, 1H, C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 15.3, 28.4, 60.9 (q, J = 36.5 Hz, OCH_2), 64.7, 118.3, 121.0, 124.7, 127.7, 128.0, 128.4, 128.5, 128.6, 128.7, 129.6, 129.7, 130.0, 130.1, 133.1, 135.0, 136.7, 143.0, 144.6, 166.8, 169.1; HR-MS (ESI) Calcd for $C_{27}H_{25}F_3NO_3$ $[M+1]^+$ 468.17791. Found 468.17810, Calcd for $C_{27}H_{24}F_3NNaO_3$ $[M+Na]^+$ 490.15998. Found 490.16005.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.096.

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