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BF_3·OEt_2-TFAA Mediated Tetra-Functionalization of Amino Acids - Synthesis of Di- and Tri-Substituted 2-Trifluoromethyl Oxazoles in One Pot

Velusamy Karuppusamy and Andivelu Ilangovan*

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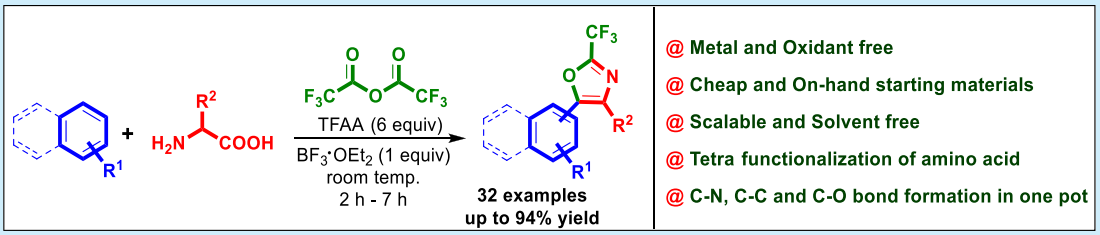

ABSTRACT: A highly efficient, TFAA-BF_3·OEt_2 mediated multicomponent coupling of amino acid, TFAA, and aromatics provides a broad library of 2-trifluoromethyl equipped 2,5-disubstituted/2,4,5-trisubstituted oxazoles or *N*-(trifluoroacetyl)-*β*-aminoalkyl ketones. This amino acid tetra-functionalization approach involves amidation (C−N), anhydride (C−O), Friedel−Crafts acylation (C−C), and Robinson−Gabriel annulation (C−O) followed by dehydrative aromatization. This reaction takes place under operationally simple, mild, and metal-free conditions using readily available amino acids and aromatic compounds.

At present, about 20% of pharmaceuticals and 30% of agrochemicals available in the market are equipped with fluorine atoms.[1] The trifluoromethyl ($-CF_3$) group shows unique characteristics such as high electronegativity, metabolic stability, lipophilicity, and bioisosteric properties for several atoms or groups.[2] Several pharmaceuticals,[3] agrochemicals,[4] and materials[5] containing the $-CF_3$ group shows interesting physical and biological properties.[3] Hence, chemists are taking a special interest in designing methods for synthesis of compounds having the $-CF_3$ group. Consequently, many methods have been developed for the incorporation of the $-CF_3$ group using reagents bearing CF_3^+,[6] CF_3^-,[7] and $CF_3^\bullet$.[8]

Oxazoles are privileged motifs found among a wide variety of pharmaceuticals,[9] natural products,[10a,b] agrochemicals,[10c] and fluorescent dyes.[10d] The approaches adopted for synthesis of functionalized oxazole could be roughly classified into three categories.[11] The most used approach is cyclization involving *α*-acylaminoketone/*α*-acyloxyketone/*α*-haloketone, primary amide/alkyne and nitrile/amine, and *α,β*-unsaturated carbonyls. The next one is regioselective functionalization of the oxazole core through metalations and subsequent functionalization.[12] The third and least explored category is the multicomponent reactions, which are highly efficient and atom economical.[11] Dehydrative condensation to form 5-(triazinyloxy) oxazoles from carboxylic acids, amino acids, and DMT-MM, followed by Suzuki−Miyaura coupling, to provide 2,4,5-trisubstituted oxazoles has already been reported.[11] Although $-CF_3$ substituted oxazoles find promising applications, very few methods are known for their synthesis.[13] These methods are associated with disadvantages such as multistep synthesis of starting material (Figure 1b),[13c,d] need for multiple reagents,[13c,d] less yield of product, and involvement of harsh reaction conditions (Figure 1c).[13e] Thus, these limitations prompted us to develop an efficient method.

Amino acids are renewable, and their racemic or natural forms are cheap and readily available in varieties. The main challenge in using amino acids in Friedel−Crafts acylation is self-coupling, on activation of the acid group. Thus, only *N*-TFA protected *α*-amino acid chloride with $AlCl_3$[14] and *N*-TFA protected *α*-amino acid *N*-hydroxysuccinimide ester (1 equiv) with $AlCl_3$ (6 equiv) were used in the Friedel−Crafts acylation of aromatics (300 equiv).[15a] Interestingly, an amino acid, on treatment with TFAA, afforded $-CF_3$ substituted oxazolone (Figure 1a).[15b]

We envisaged that if cascade tetra-functionalization of amino acids, such as amidation, anhydride formation, Friedel−Craft acylation of aromatics using the *in situ* generated amido anhydride, and intramolecular cyclization of *N*-(trifluoroacety1)-*α*-aminoalkyl ketones, could be performed in one pot, it should lead to the formation of $-CF_3$ armed oxazoles. In this

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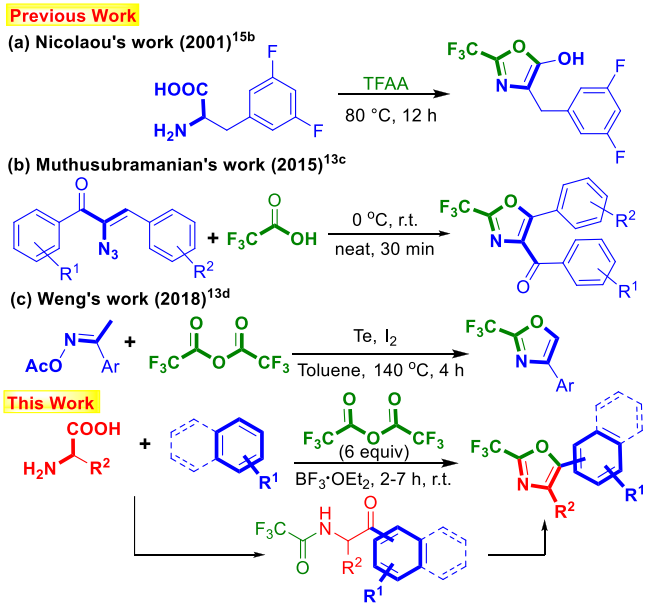
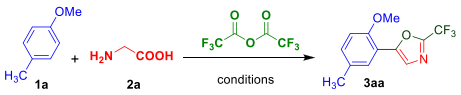


Figure 1. Synthesis of $-CF_3$ substituted oxazole.

direction, $BF_3{\cdot}OEt_2$[16]-TFAA has been discovered as the suitable reagent to mediate the cascade of all these reactions in one pot and lead to the formation of 2-(trifluoromethyl) di- or trisubstituted oxazoles or *N*-trifluoroacylamino-*β*-ketones. Herein we present the results.

The study began with identification of *p*-methylanisole (**1a**) and glycine (**2a**) as model substrates. With the aim of activating the acid through formation of anhydride and protecting the amine and using it *in situ* in Fridel–Crafts acylation, glycine **2a** (1.0 mmol) was treated, in three separate reactions with acetic anhydride (**AA**, 6.0 mmol), pivolyl chloride (**PC**, 6.0 mmol), and TFAA (6.0 mmol) for 1 h, followed by the addition of **1a** (1.0 mmol) and $AlCl_3$ (4.0 mmol) at room temperature (Table 1). In the case of **PC** and **AA**, the reaction mixture was not homogeneous and on

Table 1. Reaction Optimization[a]



entry	catalyst (mmol)	solvent	time (h)	yield **3aa** (%)[b]
1	$AlCl_3$ (4.0)	neat	3	20/NR[c,d]
2	$AlCl_3$ (1.0)	neat	3	10
3	$AlCl_3$ (4.0)	$CHCl_3$	3	15
4	$SnCl_2$ (4.0)	neat	3	trace
5	$TiCl_4$ (4.0)	neat	4	ND
6	$BF_3{\cdot}OEt_2$ (4.0)	neat	5	94
7	**$BF_3{\cdot}OEt_2$ (1.0)**	**neat**	**5**	**94**
8	$BF_3{\cdot}OEt_2$ (0.5)	neat	5	65
9	$BF_3{\cdot}OEt_2$ (0.1)	neat	5	40
10	$BF_3{\cdot}OEt_2$ (1.0)	DCM	5	80
11	$BF_3{\cdot}OEt_2$ (1.0)	$CHCl_3$	5	79
12	$BF_3{\cdot}OEt_2$ (1.0)	DCE	5	80
13	CF_3SO_3H (1.0)	neat	3	81
14	CF_3SO_3H (0.1)	neat	3	30

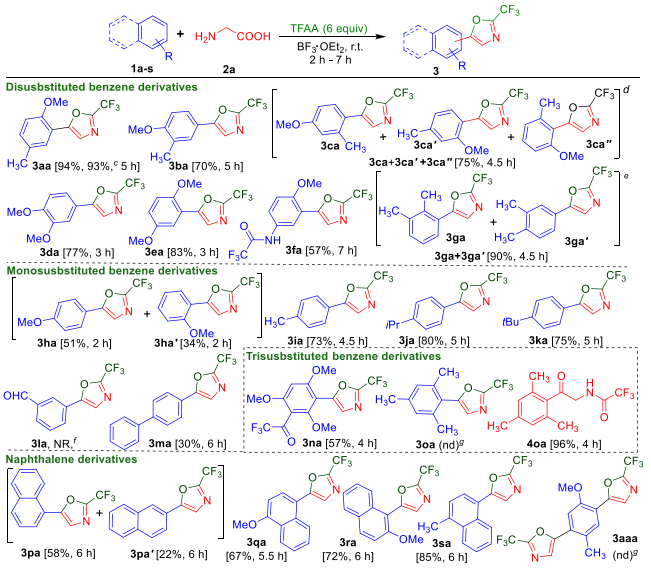
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), TFAA (6.0 mmol) at room temperature. [b]Isolated yield. [c]Pivolyl chloride. [d]Acetic anhydride, NR = No Reaction, ND = Not determined.

treatment with **1a** no reaction was observed, even after 3 h (entry 1). However, in the case of TFAA (6.0 mmol) we were delighted to observe a domino reaction leading to the formation of $-CF_3$ containing disubstituted oxazole **3aa**, albeit in low yield (20%, entry 1).

Based on this encouraging result, efforts were made to improve the yield of the product **3aa**, and the results are summarized in Table 1. On decreasing the quantity of $AlCl_3$ (1.0 mmol), the yield dropped (entry 2, 10%). The reaction performed in $CHCl_3$ medium produced **3aa** in low yield (entry 3, 15%). Since reaction without solvent produced a similar yield, further experiments were performed under neat conditions. With $SnCl_2$, only a trace amount of desired oxazole **3aa** (entry 4) was obtained. In the case of $TiCl_4$, multiple products along with **3aa** were observed and could not be separated (entry 5). Gratifyingly, when $BF_3{\cdot}OEt_2$ (4.0 mmol) was used as the catalyst, oxazole **3aa** was obtained in excellent yield (entry 6, 94%). On using 1.0 mmol of $BF_3{\cdot}OEt_2$ the yield of **3aa** did not decrease (entry 7, 94%). Further, with a substoichiometric amount of $BF_3{\cdot}OEt_2$ (entry 8, 65%; entry 9, 40%) the yield of **3aa** decreased drastically. Performing the reaction using $BF_3{\cdot}OEt_2$ (1.0 mmol) in chlorinated solvents decreased the yield (entries 10–12). Bronsted acid TfOH was also useful, but produced oxazole **3aa** in a relatively lower yield than $BF_3{\cdot}OEt_2$ (entry 13, 81%; entry 14, 30%). Based on the screening results, it was identified that the reaction of an equimolar mixture of **1a** and **2a** with 6.0 mmol of TFAA in the presence of Lewis acid $BF_3{\cdot}OEt_2$ (1.0 mmol), under solvent-free conditions and at room temperature, would be optimal for further study. After establishing the optimal conditions, the scope of the reaction of **2a** with various substituted aromatics **1a–s** was explored (Scheme 1).

Similar to **1a**, different disubstituted aromatics were examined. *o*-Methyl anisole (**1b**) furnished $-CF_3$ bearing oxazole **3ba** in good yield. But *m*-methyl anisole (**1c**), as a

Scheme 1. Scope of Electron-Rich Aromatics[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), TFAA (6.0 mmol), $BF_3{\cdot}OEt_2$ (1.0 mmol) at room temperature. [b]Isolated yield. [c]25 g scale experiment. [d]Regioisomeric ratio by NMR (44:40:16). [e]Regioisomeric ratio by NMR (42:58). [f]No reaction (**1l** was completely recovered). [g]Not detected.

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result of the *o*- and *p*-directing effect, gave a regioisomeric mixture of oxazoles, **3ca**, **3ca′**, and **3ca′′** (44:40:16), in 75% yield and only oxazole **3ca** could be isolated. Further, *o*- and *p*-methoxy anisoles **1d** and **1e** produced the corresponding $-CF_3$ substituted oxazoles **3da** (77%) and **3ea** (83%) in very good yield. The structure of **3ea** was confirmed using single crystal X-ray structure analysis [CCDC number: 1997398; see Supporting Information]. *p*-Acetamido anisole (**1f**) underwent both oxazole formation and $-COCH_3$ replacement by the $-COCF_3$ group to afford product **3fa** in moderate yield (57%). However, *o*-xylene (**1g**) afforded an inseparable regioisomeric mixture (41:59) of **3ga** and **3ga′** in excellent yield.

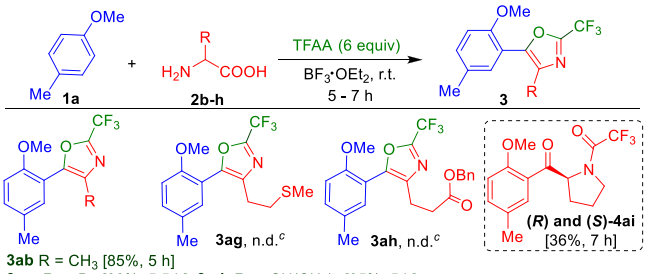
Next, reactivity of monosubstituted benzenes was examined. Anisole (**1h**) provided separable mixture of oxazoles **3ha** (51%) and **3ha′** (34%) in good overall yield. In case of toluene (**1i**), formation of CF_3-incorporated oxazole **3ia** was achieved in good yield. Similarly, oxazoles **3ja** and **3ka** were obtained in good yield by using isopropylbenzene (**1j**) and *tert*-butylbenzene (**1k**) respectively. Crude ^{1}H NMR spectra of **3ja** and **3ka** confirm the formation of only *para*-substituted oxazole. While benzaldehyde (**1l**) containing the electron-withdrawing $-CHO$ group did not undergo reaction to provide expected oxazole **3la**, biphenyl (**1m**) furnished oxazoles **3ma** in low yield.

Subsequently, reactivity of trisubstituted benzenes was examined. Intriguingly, 1,3,5-trimethoxybenzene (**1n**), due to remarkable electron richness, underwent trifluoroacetylation in addition to oxazole formation to provide **3na**. Unexpectedly, mesitylene (**1o**) containing sterically hindering trimethyl substituents provided *α*-acylamino ketone **4oa** exclusively in 96% yield, instead of expected cyclized product **3oa**. Formation of uncyclized product **4oa** was in accordance with the observation by Wasserman et al.[17b] that the amide oxygen of *α*-acylamino ketone should be retained in the oxazole formation. Interestingly, although amide carbonyl in **4oa** could undergo enolization, the steric hindrance by the 2,6-dimethyl group prevents its intramolecular nucleophilic attack on the ketone carbonyl. Further, this also provides evidence that the other possible reaction, the ketone carbonyl undergoing enolization followed by intramolecular nucleophilic attack on the less hindered amide carbonyl, does not take place.[17b] Simple benzene did not undergo this reaction. Next, naphthyl ring system compounds were studied. A separable regioisomeric mixture of oxazole **3pa** (58%) and **3pa′** (22%) was obtained from naphthalene (**1p**) in good yield. 1-Methoxynaphthalene (**1q**) provided oxazole **3qa** in good yield. Substituted oxazoles **3ra** and **3sa** were obtained in good yield from corresponding 2-methoxy naphthalene (**1r**) and 1-methyl naphthalene (**1s**) respectively.

We expected that employing 2.0 mmol of amino acid **2a** and 1.0 mmol of aryl compound **1a** may yield 2-fold oxazole-introduced product **3aaa**. However, only single oxazole substituted product **3aa** was obtained. Compound **3aa** obtained in 93% yield (48.9 g) from reaction of **1a** (25.0 g) and **2a** (15.3 g) under standard condition guarantees applicability of this method in bulk scale (Scheme 1).

Having successfully observed oxazole formation on different aromatic substrates **1a**–**s** using glycine (**2a**), the reactivity of different *α*-amino acids **2b**–**h** were examined next. Aromatic compound **1a** was taken as standard (Scheme 2) and treated with L-alanine (**2b**) to obtain 2-CF_3 containing trisubstituted oxazole **3ab** in excellent yield. Similarly, oxazole **3ac** and **3ad**

Scheme 2. Substrate Scope of *α*-Amino Acids[a,b]



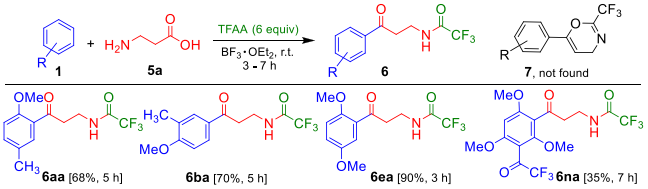
3ab R = CH_3 [85%, 5 h]
3ac: R = -Bn [80%, 5.5 h], **3ad:** R = -$CH(CH_3)_2$ [85%, 5 h],
3ae: R = -$CH_2CH(CH_3)_2$ [82%, 6 h], **3af:** R = -$CH(CH_3)CH_2CH_3$ [80%, 6 h]

[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), TFAA (6.0 mmol), BF_3·OEt_2 (1.0 mmol) at room temperature. [b]Isolated yield. [c]Not detected.

were obtained from 3-phenyl-L-alanine (**2c**) and L-valine (**2d**) respectively in good yield. Oxazole **3ae** and **3af** were obtained in good yield when **1a** was treated with L-leucine (**2e**) and L-isoleucine (**2f**) respectively. Unfortunately, methionine (**2g**) and 2-amino-5-(benzyloxy)-5-oxopentanoic acid (**2h**) failed to give the desired oxazoles **3ag** and **3ah** respectively. Interestingly, L-proline (**2i**) underwent *N*-acylation followed by Fridel–Craft's *C*-acylation to provide optically pure *α*-acylamino ketone (*S*)-**4ai** in moderate yield. Similalrly, D-proline also provided optically pure (*R*)-**4ai** in similar yield. This confirms no racemization occurs during the reaction.

Next, the reactivity of *β*-amino acids, with activated aromatics, were examined under the standardized reaction conditions (Scheme 3). *β*-Alanine (**5a**), on treatment with **1a**,

Scheme 3. Substrate Scope of *β*-Alanine[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **5a** (1.0 mmol), TFAA (6.0 mmol), BF_3·OEt_2 (1.0 mmol) at room temperature. [b]Isolated yield.

afforded the Mannich base[17a] *N*-trifluoroacetylamino-*β*-ketone **6aa** instead of expected six-membered CF_3-group bearing 6-aryl-2-trifluoromethyl-4*H*-[1,3]oxazine **7**. Similarly, reaction of **1b** and **1e** with **5a** gave the corresponding products **6ba** and **6ea** respectively. However, electron-rich but sterically hindered aromatic substrate **1n** on reaction with **5a** provided *N*-trifluoroacylamino-*β*-ketone **6na**, albeit in low yield, in which trifluoroacetylation occurred on the aryl ring.

In order to understand the mechanism of this cascade reaction, control experiments were performed. Formation of mono-functionalized amino acid (**8a**, 92%, Scheme 4a) as an intermediate was confirmed by treating amino acid **2a** with TFAA (1.2 equiv) and quenching with H_2O.

Involvement of anhydride as an intermediate was confirmed through formation of methyl ester (**8b**, 85%, Scheme 4a) by treating amino acid **2a** with TFAA (3.0 equiv) and entrapping it with methanol. The reaction between **1e** and **2a** when worked up quickly before completion (20 min) provided 25% of keto amide **4ea**, along with 40% of **3ea** (Scheme 4b). This confirms that keto amide **4ea** is an intermediate in the reaction.

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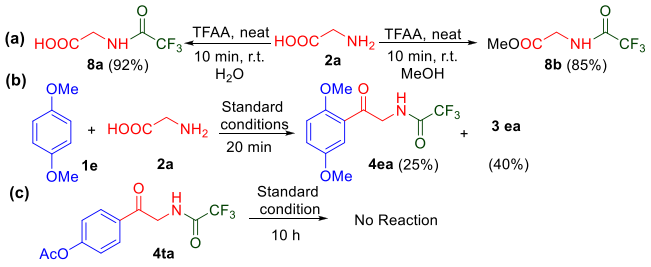
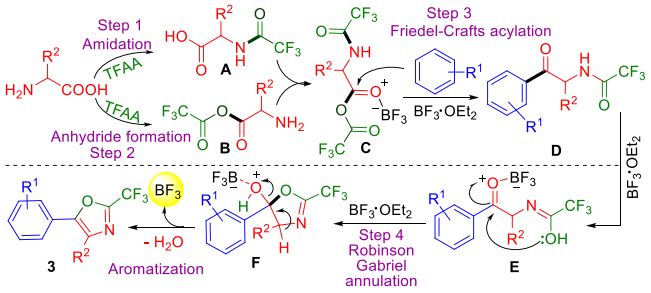
Scheme 4. Control Experiments



Further, compound **4ta** containing the electron-withdrawing 4-OAc group failed to undergo cyclization to form oxazole (Scheme 4c). The electron-withdrawing effect of the 4-OAc due to its influence on the aromatic ring disfavors positive polarization of ketone carbonyl carbon; hence, nucleophilic attack by the amide carbonyl oxygen is not facilitated.

Based on the results obtained and literature precedence,[17b] a plausible mechanism is proposed as shown in Scheme 5.

Scheme 5. Proposed Mechanism



Reaction of an α-amino acid with TFAA forms *N*-trifluoroacetamide **A** and mixed anhydride **B** which ultimately gives an amido anhydride **C** from steps 1 and 2. BF_3 should facilitate Friedel–Crafts acylation of aromatics with intermediate **C** to form intermediate **D**. Enolisation of **D** to form **E**[17b] should facilitate intramolecular Robinson Gabriel annulation and aromatization of intermediate **F** to afford $-CF_3$ substituted oxazole **3**. As explained in the case of α-acylamino ketone **4oa**, the other possible pathway, ketone carbonyl undergoing enolization and nucleophilic attack on the amide carbonyl, is not favored.[17b]

In summary, we have developed a novel and simple multicomponent approach for the formation of $-CF_3$ containing di- and trisubstituted oxazoles as well as *N*-trifluoroacylamino-β-ketones in one pot from readily available amino acids. The starting material, amino acids, are cheap in racemic and natural forms, found in varieties, and renewable. Unlike other methods, this is versatile, so that di- as well as trisubstituted $-CF_3$ containing oxazoles could be obtained in excellent yields, and has a good substrate scope. The reaction conditions are metal-free, eco-friendly, and mild. Thus, from this study we were able to observe TFAA/BF_3·OEt_2 mediated, cascade amidation and anhydride formation with amino acids, Friedel–Craft acylation on the aromatic ring, *in situ* intramolecular Robinson–Gabriel cyclization, and aromatization of *N*-(trifluoroacety1)-α-aminoalkyl ketones leading to the formation of a variety of 2-CF_3 containing oxazoles. To the best of our knowledge, such an unprecedented tetra-functionalization of amino acids is observed for the first time. This method successfully avoids self-coupling of amino acids. We strongly believe that this easily scalable new synthetic method would find immense use in medicinal chemistry, material science, and industry. Further, biological studies of the synthesized compounds are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02484.

Experimental procedures, characterization data, copies of NMR spectra for all new products, and HPLC chromatograms of **4ai** (PDF)

Accession Codes

CCDC 1997398 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Andivelu Ilangovan − *School of Chemistry, Bharathidasan University, Tiruchirappalli 620024, India;* orcid.org/0000-0001-7240-7166; Email: ilangovanbdu@yahoo.com

Author

Velusamy Karuppusamy − *School of Chemistry, Bharathidasan University, Tiruchirappalli 620024, India; Department of Pharmaceutical Research & Development, Biocon Limited, Bangalore 560100, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02484

Notes

The authors declare no competing financial interest.

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