A Facile Synthesis of New L-Proline-Based Trifluoromethyl Oxazole Derivatives Using Microwave Irradiation and Conventional Method

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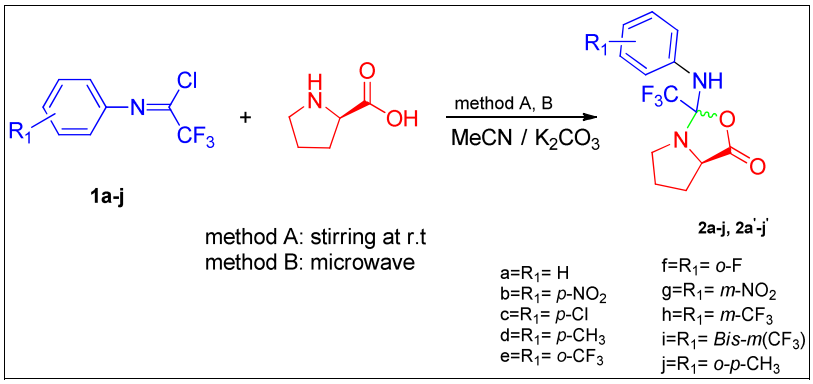

Cyclization reaction of L-proline with trifluoroacetimidoyl chlorides has been developed as an efficient strategy for the synthesis of trifluoromethyl oxazole derivatives by two methods: (a) in the presence of K_2CO_3 as a base in acetonitrile at room temperature and (b) in the presence of K_2CO_3 as a base in acetonitrile using microwave irradiation, in one pot reaction. The microwave irradiation has been found to be the most efficient method. High yields and short reaction times were obtained for both electron-releasing and electron-withdrawing substituted *N*-aryltrifluoroacetimidoyl chloride derivatives by microwave irradiation.

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INTRODUCTION

Oxazolidone is a heterocyclic organic compound that is particularly attractive because it is known to be the core structural unit of compounds widely used in pharmaceutical agents such as antibacterial [1], antiallergy [2], immunosuppressant [3], and synthetic chemistry [4]. *N*-Aryl oxazolidones have attracted a great deal of attention as a new class of orally active synthetic antibacterial agents with activity against gram-positive and anaerobic bacteria [5]. It is known that the introduction of fluorine atom into organic compounds greatly changes their biological activities [6]. Thus, development of effective methods for the contraction of fluorinated oxazolidone frame work could be of interest in organic synthesis and pharmacological agents [7].

Recently, organofluorine compounds have attracted huge interest in the pharmaceutical and agrochemical industries [8]. In particular, trifluoroacetimidoyl chloride-substituted molecules have become a subject of intense investigation [9], because fluorinated building blocks exhibit interesting biological activity [10]. Trifluoromethylated compounds have attracted considerable attention due to the influence of fluorine atoms, they often furnish organic molecules with unique properties that cannot be attainted using any other element [11]. In our previous paper, aryl trifluoroacetimidoyl chlorides were used for the synthesis of new piperazinylquinolone, which displayed good antibacterial activities [12,13]. *N*-Aryltrifluoroacetimidoyl halides are the most useful trifluoromethylated synthetic blocks among fluorine compounds [14], because these compound have potentially active sites, such as C–N double bonds, halogens, *N*-aryl, and CF_3 groups [15,16].

Microwave irradiation (MWI) has been an available method in organic synthesis and chiral oxazolines, which has been applied in heterocycle chemistry and cycloaddition reaction [17,18]. Microwave irradiation has certain benefits over conventional heating such as the acceleration of reaction rate, milder reaction conditions, higher yield, lower energy consumption, enhancement of the selectivity of reaction, and easier workup. Although there are many methods for the preparation of oxazole compounds, and the synthesis of different oxazole triflouromethylated derivatives have been reported in literature [19–22], we did not see any reports for synthesis of aryl-3-(trifluoromethyl) tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one derivatives. Continuing our studies [12,13], we now report the synthesis of aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one derivatives using the reaction of trifluoroacetimidoyl chloride derivatives with L-proline by two methods: (a) in the presence of K_2CO_3 as a base in acetonitrile at room temperature and (b) in the presence of K_2CO_3 as a base in acetonitrile using microwave irradiation, in one pot reaction. We did not see any report for the synthesis of these

compounds in the literatures. We hope these compounds to be useful for biological activities.

RESULTS AND DISCUSSION

Trifluoromethylated compounds are of particular interest, as the strong electron-withdrawing effect of the CF_3 group contributes to a number of biologically important molecular properties [19,23].

Also CF_3-substituent, acting as a stabilizing polar group in oxazoline ring and prevent the ring from opening because of its strong electron-withdrawing effect. In this research, to increase the interesting and remarkable biological activities of oxazolones, we required the synthesis of the oxazolones-annulated trifluoromethyl derivative with the following structure (Scheme 1).

Therefore, in order to synthesize stable and biologically active oxazole derivatives, we selected L-proline as a nucleophile in the cyclization reaction with trifluoroacetimidoyl chlorides under mild conditions.

Trifluoroacetimidoyl chlorides (**1a–j**) have been prepared by refluxing a mixture of trifluoroacetic acid and primary amines in carbon tetrachloride in the presence of triethylamine and triphenylphosphine by one pot reaction [24,25].

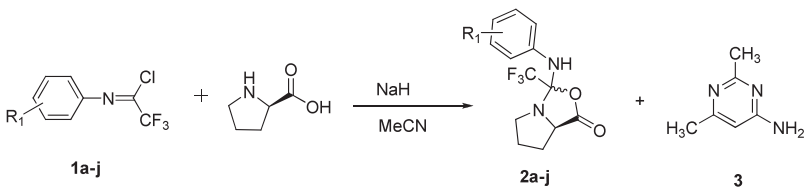
In an initial study, we examined the reaction of acetymidoyl chloride (**1a**) with L-proline in the presence of NaH in acetonitrile under ambient temperature. In this case, the purification of products is difficult, and the obtained yields are low. After the purification and identification of the product by IR, ^{1}H-NMR, ^{13}C-NMR, and X-ray, 2,6-dimethylpyrimidin-4-amine (**3**) was obtained as the main product. Under these conditions, in addition to the reaction of imidoyl chlorides **1a** with L-proline, in the presence of NaH, three molecules of acetonitrile were condensed to produce compound **3** (Scheme 1) [26]. The single-crystal X-ray analyses confirm the structure of the 2,6-dimethylpyrimidin-4-amine (**3**).

Further attempts were made to improve the yields. First, the reaction was carried out in the presence of K_2CO_3 in acetonitrile at ambient temperature under an N_2 atmosphere for 8–12 h. It afforded the corresponding products **2a–j** in good yields (70–82%) (Scheme 2, Table 1). In this reaction, chlorine atom of the trifluoroacetimidoyl chloride is replaced by pyrrolidine ring to give the substitution products, and then cyclization occurs by COO– group.

After optimizing conditions (ambient temperature, acetonitrile as a solvent, and K_2CO_3), in order to improve the yields and decrease the reaction time, we used the microwave-assisted method for the synthesis of aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2a–j**), in the presence of K_2CO_3 in acetonitrile (Scheme 2). L-Proline-based trifluoromethyl oxazole compounds were synthesized by microwave irradiation (MW) as well as conventional stirring with potassium carbonate in acetonitrile as solvent.

We synthesized the new aryl-3-(trifluoromethyl) tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-ones (**2a–j**) (Scheme 1, Table 1) derivatives under microwave irradiation as well as the conventional method. However, as shown in Table 1, using microwave irradiation normally preceded in improved yields compared with the previous method, and with the obvious advantage of a faster and more convenient operation. A possible reaction mechanism is illustrated in Scheme 3.

Scheme 1. Reaction of acetymidoyl chlorides with L-proline in the presence of NaH in acetonitrile under ambient temperature.



Scheme 2. Synthesis of various aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one in acetonitrile in present of K_2CO_3 as a base using microwave irradiation and conventional method.

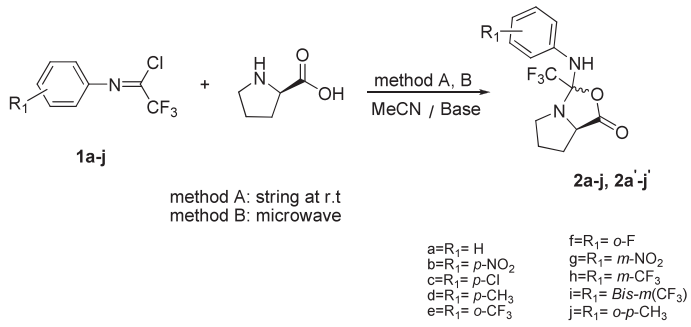
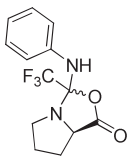
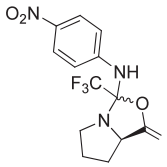
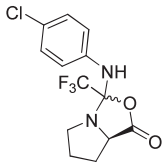
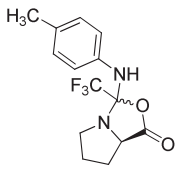
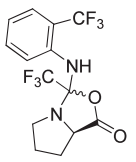


Table 1

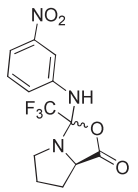
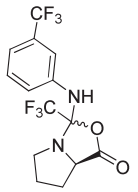
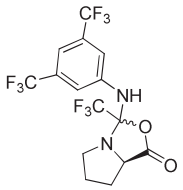
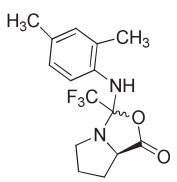
Synthesis of various aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one.

				Condition A stirring at room temperature		Condition B MWI[b] (50°C, 400 W)	
Entry	R_1	Product	Base	Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	H	 **2a,2a'**	K_2CO_3	12	64	20	69
2	*p*-NO_2	 **2b, 2b'**	K_2CO_3	8	82	20	95
3	*p*-Cl	 **2c,2c'**	K_2CO_3	8	77	20	92
4	*p*-CH_3	 **2d, 2d'**	K_2CO_3	12	76	20	85
5	*o*-CF_3	 **2e,2e'**	K_2CO_3	8	88	20	90
6	*o*-F	 **2f, 2f'**	K_2CO_3	8	82	20	86

(*Continued*)

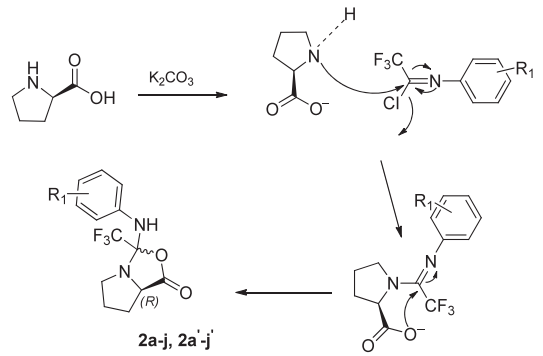
Table 1

(*Continued*)

				Condition A stirring at room temperature		Condition B MWI[b] (50°C, 400 W)	
Entry	R_1	Product	Base	Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
7	*m*-NO_2	 **2g,2g'**	K_2CO_3	8	80	20	92
8	*m*-CF_3	 **2h,2h'**	K_2CO_3	8	70	20	87
9	Bis-*m*(CF_3)	 **2i,2i'**	K_2CO_3	8	89	20	98
10	*o*-*p*-CH_3	 **2j, 2j'**	K_2CO_3	12	75	20	88

[a]Isolated yields after purification by plate chromatography.
[b]Microwave irradiation.

Scheme 3. A possible mechanism for the synthesis of aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one.



The yields of these reactions were generally excellent. It is important to note that the presence of an electron-withdrawing group had no effect on the yield. Under the optimized conditions, various acetymidoyl chlorides with electron-donating or electron-withdrawing groups reacted to give the corresponding aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one products in excellent yields (Table 1).

Synthesis of various aryl-3-(trifluoromethyl) tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one. The reaction of trifluoroacetimidoyl chlorides (**1a–j**) with L-proline in the presence of K_2CO_3 in acetonitrile using both microwave irradiation and conventional method gave an isomeric mixture of two diastereomers, (3*R*,7*aR*)-3-

(arylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one and (3*S*,7*aR*)-3-(arylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (Scheme 1).

The generality of this method was investigated by utilization of ten various acetymidoyl chlorides in the reaction to furnish corresponding trifluoromethyl oxazole derivatives in good to excellent yield. The reaction of **1a**, **1b**, **1c**, **1e**, **1g**, **1h**, and **1i** with L-proline in acetonitrile gave an diastereomeric mixture (3*R*/3*S*,7*aR*)-3-(phenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2a**, **2a′**) for **1a**, (3*R*/3*S*,7*aR*)-3-(4-nitrophenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2b**, **2b′**) for **1b**, (3*R*/3*S*,7*aR*)-3-(4-chlorophenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2c**, **2c′**) for **1c**, (3*R*/3*S*,7*aR*)-3-(trifluoromethyl)-3-(2-(trifluoromethyl)phenylamino) tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one(**2e**, **2e′**) for **1e**, (3*R*/3*S*,7*aR*)-3-(3-nitrophenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*] oxazol-1(3H)-one (**2g**, **2g′**) for **1g**, (3*R*/3*S*,7*aR*)-3-(trifluoromethyl)-3-(3-(trifluoromethyl)phenylamino) tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2h**, **2h′**) for **1h**, and (3*R*/3*S*,7*aR*)-3-(3, 5-bis(trifluoromethyl)phenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2i**, **2i′**) according to the ^{1}H-NMR spectra. Also, when **1d**, **1f**, and **1j** trifluoroacetimidoyl chloride derivatives were employed, corresponding trifluoromethyl oxazole compounds as a diastereomeric mixture were obtained. In these reactions, we could not obtain diastereomeric ratio, because the ^{1}H-NMR spectrum of the compounds **2d**, **2f**, and **2j** showed three multiplet signals at δ, 4.12–4–15, 4.23–4.25, and 3.55–3.57 ppm, respectively, corresponding to the H HCNCOO group.

Each of the two diastereomers, (**2a**, **2a′**), (**2b**, **2b′**), (**2c**, **2c′**), (**2d**, **2d′**), (**2e**, **2e′**), (**2fc**, **2fc′**), (**2g**, **2g′**), (**2h**, **2h′**), (**2i**, **2i′**), and (**2j**, **2j′**), showed the same Rf value on thin-layer chromatography (TLC). However, the ^{1}H-NMR spectrum of the mixture showed the H HCNCOO signal as two singlets at δ major = 5.63, δ minor = 4.11 ppm for (**2a**, **2a′**); δ major = 4.14, δ minor = 4.04 ppm for (**2b**, **2b′**); δ major = 4.79, δ minor = 4.24 ppm for (**2c**, **2c′**); δ major = 4.92, δ minor = 4.70 ppm for (**2e**, **2e**); δ major = 4.80, δ minor = 4.58 ppm for (**2g**, **2g′**); δ major = 4.96, δ minor = 4.80 ppm for (**2h**, **2h′**); and δ major = 6.61, δ minor = 5.55 ppm for (**2i**, **2i′**), which is characteristic of trifluoromethyl oxazoles. The Fourier transform IR, ^{19}F-NMR, ^{1}H-NMR, ^{13}C-NMR, correlation spectroscopy, and heteronuclear multiple bond correlation spectra and elemental analysis confirmed the structures of the products.

The IR spectrum of (3*R*/S, 7*aR*)-3-(3-nitrophenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (**2g**) showed absorption bands at 3433 and 3408 cm^{-1}, corresponding to –NH stretching, and at 1719 cm^{-1}, corresponding to the C=O moiety. The ^{1}H-NMR spectrum of **2g** showed a signal at δ 10.89 corresponding to the NH group, a signal at δ 8.31, a doublet at δ 7.93 (J = 7.8 Hz), and a doublet at δ 7.87 (J = 8.1 Hz), due to the aromatic protons. Also the ^{1}H-NMR spectrum of **2g** showed two multiplets at δ 4.77–4.84 and δ 4.57–4.60 corresponding to the –CH (two diastereotopic CH) and three multiplets at δ 3.57–3.74, δ 2.23–2.29, and δ 1.82–1.85, corresponding to the pyrrolidine ring protons. The ^{13}C-NMR spectrum of **2g** showed downfield signal at δ 170.50 ppm for the carbonyl group and at δ 22.70, 25.70, 29.50, and 62.2 ppm for the three CH_2 and CH carbons, respectively. The ^{19}F-NMR spectrum of **2g** in dimethyl sulfoxide (DMSO) showed two peaks at δ −76.94 and −76.96 for the CF_3 group.

CONCLUSION

In conclusion, we have successfully synthesized a series of new aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one derivatives using different 2, 2, 2-trifluoro-*N*-arylacetimidoyl chlorides under mild conditions. In addition to its efficiency, simplicity, and mild reaction conditions, this method provides high yields of trifluoromethyl oxazole. Therefore, this protocol is efficient and may open up a new area for the synthesis of trifluoromethylated oxazoles. Further studies including the pharmacological activities in this area are being carried out in our laboratory.

EXPERIMENTAL

General. All manipulations were carried out under a nitrogen atmosphere; all reactions were performed with magnetic stirring in flame-dried glassware with dry and distilled solvents. Chemicals and solvents were purchased from Merck AG and Aldrich Chemical companies (Merck and Aldrich Representation in Tehran). Melting points were determined with a Barnstead electrothermal (Dubuque, IA). IR spectra (KBr, Neat) were obtained on a Thermo Scientific, Nicolet iS10 Fourier transform IR spectrometer (Thermo Fisher Scientific, Waltham, MA). ETHOS 1 Advanced Microwave Digestion System (Milestone, Italy) was used for the synthesis of compounds. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded by a Bruker DRX-400 or -300 AVANCE spectrometer at 400 or 300 and 100 or 75 MHz (Bruker, Billerica, MA), respectively, using Me_4Si as an internal standard (chemical shifts in δ, ppm). ^{19}F-NMR spectra were taken on Brucher AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. Element analyses (CHN) were performed with a EuroVector EuroEA3000 CHNSO analyzer (EuroVector, Milan). Merck silica-gel 60F254 plates were used for analytical TLC.

General procedure for the synthesis of 3-aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one derivatives. A representative experimental procedure is described as follows. Method A: a mixture of L-proline (1 mmol) and calcium carbonate (2 mmol) in dry acetonitrile (10 mL) was stirred at room temperature for 20 min. Imidoyl (1 mmol) in dry acetonitrile (10 mL) was added dropwise to this mixture. The reaction mixture was then stirred at room temperature and monitored by TLC (EtOAc/*n*-hexane). After the completion of the reaction at 8–12 h, the solvent was removed under reduced pressure. The crude product was purified by TLC plates (silica-gel, appropriate EtOAc/hexane) to give a diastereomer mixture of (3*S*,7*aR*) and (3*R*,7*aR*) 3-aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one.

Method B: A mixture of L-proline (1 mmol), calcium carbonate (2 mmol), and imidoyl (1 mmol) in dry acetonitrile (10 mL) was charged in a pressure-tight microwave tube containing a stirring bar. The reaction mixture was submitted to microwave irradiation for 20 min at 50°C, with an irradiation power of 400 W. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by TLC plates (silica-gel, appropriate EtOAc/hexane) to give a diastereomer mixture of (3*S*,7*aR*) and (3*R*,7*aR*) 3-aryl-3-(trifluoromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one.

(3R/3S,7aR)-3-(Phenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2a, 2a'). The product was purified by TLC plates (*n*-hexane/EtOAc, 1:1) to give product as a yellow oil, which was found to be a mixture of two diastereomers 56:44; diastereomeric ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 5.63, δ minor = 4.11; with the same Rf (*n*-hexane/EtOAc, 1:1). ^{1}H-NMR (400 MHz, DMSO): δ = 1.14–1.29 (m, 6CH_2, 12H), 4.11, 5.63 (m, 2H, diastereotopic CH–C=O), 7.07 (m, 2H, Ar), 7.31–7.50 (m, 5H, Ar), 7.62 (m, 1H, Ar), 7.82 (m, 2H, Ar), 8.00, 8.33 (br, 2H, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 25.1, 31.8, 37.9, 56.5, 114.7, 125.3, 126.5, 127.5, 129.1, 129.3, 129.4, 135.9, 173.2 (C=O). ^{19}F (282.2 MHz, DMSO): δ = −77.04, −76.87 (6 F, CF_3). *Anal.* Calcd. for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79%. Found: C, 54.52; H, 4.53; N, 9.75%.

(3R/3S,7aR)-3-(4-Nitrophenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2b, 2b'). The product was purified by TLC plates (*n*-hexane/EtOAc, 2:1) to give product as a pale white solid. Mp 141–143°C, which was found to be a mixture of two diastereomers 66:33; diastereomer ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 4.14, δ minor = 4.04; with the same Rf (*n*-hexane/EtOAc, 2:1). IR (KBr): 3325, 1743, and 1621 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO): δ = 1.03–1.07 (m, 4H, CH_2), 1.18–1.30 (m, 4H, CH_2), 2.07, 2.33, 2.67, 3.16 (m, 4H, CH_2), 4.04, 4.14 (m, 2H, diastereotopic CH–C=O), 7.95–7.98 (dd, 4H, J = 8.0, 2.4 Hz, Ar), 8.29–8.32 (dd, 4H, J = 8.0, 2.4 Hz, Ar), 11.82 (br, 2H, NH). ^{19}F (282.2 MHz, DMSO): δ = −73.91 (3 F, CF_3). *Anal.* Calcd. for $C_{13}H_{12}F_3N_3O_4$: C, 47.14; H, 3.65; N, 12.69%. Found: C, 47.12; H, 3.67; N, 12.65%.

(3R/3S,7aR)-3-(4-Chlorophenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2c, 2c'). The product was purified by TLC plates (*n*-hexane/EtOAc, 1:3) to give product as a yellow oil, which was found to be a mixture of two diastereomers 80:20; diastereomer ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 4.79, δ minor = 4.24; with the same Rf (*n*-hexane/EtOAc, 1:3). IR (thin film): 3335, 1704, and 1598 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.27–1.35 (m, 4H, CH_2), 1.98–2.01 (m, 4H, CH_2), 2.26–2.29 (m, 4H, CH_2), 4.24, 4.79 (m, 2H, diastereotopic CH–C=O), 7.31–7.33 (dd, 4H, J = 8.0, 2.40 Hz, Ar), 7.42–7.53 (dd, 4H, J = 8.0, 2.40 Hz, Ar), 8.67, 8.73 (br, 2H, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 24.61, 36.8, 55.6, 75.7, 76.1, 95.3, 95.4, 126.2, 126.4, 128.9, 131.1, 134.3, 170.9 (C=O). ^{19}F (282.2 MHz, DMSO): δ = −77.04 (3 F, CF_3). *Anal.* Calcd. for $C_{13}H_{12}ClF_3N_2O_2$: C, 48.69; H, 3.77; N, 8.74%. Found: C, 48.65; H, 3.80; N, 8.72%.

(3R/3S,7aR)-3-(p-Tolylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2d, 2d'). The product was purified by TLC plates (*n*-hexane/EtOAc, 1:1) to give product as yellow oil, which was found to be a mixture of two diastereomers with the same Rf (*n*-hexane/EtOAc, 1:1). IR (thin film): 3449, 1697, and 1516 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 0.86–0.89 (m, 2H, CH_2), 1.23 (S, 3H, CH_3), 1.27–1.31 (m, 2H, CH_2), 2.09–2.27 (m, 2H, CH_2), 4.12–4.15 (m, 2H, CH–C=O, diastereotopic protons) 7.14–7.16 (m, 2H, Ar), 7.66–7.73 (m, 2H, Ar), 10.37 (br, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 20.6, 23.4, 24.6, 36.8, 55.6, 95.3, 95.4, 124.8, 124.5, 129.3, 129.1, 132.9, 135.4, 171.0 (C=O). ^{19}F (282.2 MHz, DMSO): δ = −77.01 (3 F, CF_3). *Anal.* Calcd. for $C_{14}H_{15}F_3N_2O_2$: C, 56.00; H, 5.04; N, 9.33%. Found: C, 56.04; H, 5.10; N, 9.35%.

(3R/3S,7aR)-3-(Trifluoromethyl)-3-(2-(trifluoromethyl) phenylamino)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2e, 2e'). The product was purified by TLC plates (*n*-hexane/EtOAc, 2:1) to give pure product as a white solid. Mp 99–102°C, which was found to be a mixture of two diastereomers 71:29; diastereomer ratio as calculated from their 1H-NMR integrals CHC=O signal, δ major = 4.92, δ minor = 4.70; with the same Rf (*n*-hexane/EtOAc, 2:1). IR (KBr): 3378 and 1702 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.41–3.98 (m, 6CH_2, 12H), 4.70, 4.92 (m, 2H, diastereotopic CH–C=O), 7.36–7.77 (m, 8H, Ar), 9.38, 9.98 (br, 2H, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 24.4, 36.8, 56.1, 94.4, 121.2, 124.6, 127.5, 129.1, 129.2, 130.2, 132.6, 132.8, 134.0, 171.2 (C=O). ^{19}F (282.2 MHz, DMSO): δ = −58.75, −77.92 (6 F, 2CF_3). *Anal.* Calcd. for

$C_{14}H_{12}F_6N_2O_2$: C, 47.47; H, 3.41; N, 7.91%. Found: C, 47.45; H, 3.38; N, 7.90%,

(3R/3S,7aR)-3-(2-Fluorophenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2f, 2f'). The product was purified by washing with *n*-hexane to give product as a yellow oil, which was found to be a mixture of two diastereomers with the same Rf (*n*-hexane/EtOAc, 1:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40–3.13 (m, $3CH_2$, 12H), 4.23–4–26 (m, 2H, CH–C=O, diastereotopic protons), 6.76–6.87 (m, 8H, Ar), 7.84 (br, 2H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.74, 38.73, 45.13, 68.16, 114.91, 118.09 (CF_3, q, $J_{C\text{-}F}$ = 286 Hz), 123.13, 123.98, 128.80, 130.88, 143.76 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 32 Hz), 153.29 (C–F, d, J = 240 Hz), 175.53 (C=O). *Anal.* Calcd. for $C_{13}H_{12}F_4N_2O_2$: C, 51.32; H, 3.98; N, 9.21%. Found: C, 51.30; H, 3.95; N, 9.18%.

(3R/3S,7aR)-3-(3-Nitrophenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2g, 2g'). The product was purified by TLC plates (*n*-hexane/EtOAc, 1:3) to give pure product as a yellow oil, which was found to be a mixture of two diastereomers 81:19; diastereomer ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 4.80, δ minor = 4.58; with the same Rf (*n*-hexane/EtOAc, 1:3). IR (thin film): 3408 and 1719 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.83 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 3.62 (m, 2H, CH_2), 4.58, 4.80 (m, 2H, diastereotopic CH–C=O), 7.62 (d, 1H, J = 7.8 Hz, Ar), 7.86–7.94 (dd, 2H, J = 8.1, 7.8 Hz, Ar), 8.87 (m, 1H, Ar), 10.75 (br, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 22.7, 25.7, 29.5, 62.2, 108.2, 115.3, 120.1, 126.9, 129.8, 132.4 (q, $J_{C\text{-}C\text{-}F}$ = 43.0 Hz), 137.4, 147.8, 170.5 (C=O). ^{19}F-NMR (376 MHz, DMSO): δ = −76.96, −76.94 (6F, CF_3). *Anal.* Calcd. for $C_{13}H_{12}F_3N_3O_4$: C, 47.14; H, 3.65; N, 12.69%. Found: C, 45.14; H, 3.64; N, 12.65%.

(3R/3S,7aR)-3-(Trifluoromethyl)-3-(3-(trifluoromethyl) phenylamino)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2h, 2h'). The product was purified by TLC plates (*n*-hexane/EtOAc, 1:2) to give product as a yellow oil, which was found to be a mixture of two diastereomers 55:45; diastereomer ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 4.96, δ minor = 4.80; with the same Rf (*n*-hexane/EtOAc, 1:2). IR (thin film): 3388 and 1651 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.24–3.37 (m, $6CH_2$, 12H), 4.80, 4.96 (m, 2H, diastereotopic CH–C=O), 7.06–7.65 (m, 8H, Ar), 7.89, 7.96 (br, 2H, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 24.6, 36.7, 55.6, 116.1 (q, $J_{C\text{-}C\text{-}F}$ = 42.0 Hz), 119.5 (q, $J_{C\text{-}C\text{-}F}$ = 44.8 Hz), 127.5, 128.5, 128.7, 128.8, 131.9, 132.0, 146.5, 154.6, 172.4 (C=O). *Anal.* Calcd. for $C_{14}H_{12}F_6N_2O_2$: C, 47.47; H, 3.41; N, 7.91%. Found: C, 47.43; H, 3.35; N, 7.87%.

(3R/3S,7aR)-3-(3,5-bis(Trifluoromethyl)phenylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2i, 2i'). The product was purified by washing with *n*-hexane to give product as a brown solid. Mp 178–183°C, which was found to be a mixture of two diastereomers 70:30; diastereomer ratio as calculated from their ^{1}H-NMR integrals CHC=O signal, δ major = 6.61, δ minor = 5.55; with the same Rf. IR (KBr): 3420, 1725, and 1559 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO): δ = 1.05–3.35 (m, $6CH_2$, 12H), 5.55–6.61 (m, 2H, diastereotopic CH–C=O), 7.22–7.68 (m, 6H, Ar), 8.98 (br, 2H, NH). ^{19}F-NMR (376 MHz, DMSO): δ = −73.39, 70.00 (6F, $2CF_3$). *Anal.* Calcd. for $C_{15}H_{11}F_9N_2O_2$: C, 42.67; H, 2.63; N, 6.63%. Found: C, 42.62; H, 2.60; N, 6.60%.

(3R/3S,7aR)-3-(2, 4-Dimethylphenylamino)-3-(trifluoromethyl) tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (2j, 2j'). The product was purified by washing with *n*-hexane to give product as a solid. Mp 148–150°C, which was found to be a mixture of two diastereomers with the same Rf. IR (KBr): 3432 and 1725 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.24–1.93 (m, 4H, CH_2), 2.17, 2.30 (s, 6H, CH_3), 3.32–3.46 (m, 8H, $2CH_2$), 3.55–3.56 (m, 2H, CH–C=O, diastereotopic protons), 7.02–7.20 (m, 6H, Ar), 9.26 (m, 2H, NH). ^{13}C-NMR (100 MHz, DMSO): δ = 17.3, 20.5, 26.8, 28.0, 43.8, 82.2, 119.1, 121.85 (CF_3, q, $J_{C\text{-}F}$ = 27 8Hz), 126.1, 126.5, 127.2, 130.4, 131.9, 137.0, 145.7, 171.8. *Anal.* Calcd. for $C_{15}H_{17}F_3N_2O_2$: C, 57.32; H, 5.45; N, 8.91%. Found: C, 57.30; H, 5.40; N, 8.81%.

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