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An efficient synthesis of new 2-aminomethyl-1,3,4-oxadiazoles from enantiomeric phenylglycine hydrazides

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ABSTRACT

New derivatives of 2-aminomethyl-1,3,4-oxadiazole were synthesized in the reactions of *N*-protected phenylglycine hydrazides and triethyl orthoesters (orthoformate, orthoacetate, orthopropionate, orthobenzoate) in the presence of glacial acetic acid. Studies on the cleavage reactions of the acid-sensitive *N*-BOC and *N*-Ac 1,3,4-oxadiazoles are presented. Spectral characteristics of the compounds and attempts to elucidate the racemization phenomenon observed in products are also discussed.

1. Introduction

1,3,4-Oxadiazoles belong to a group of heterocycles that have been attracting attention for last two decades due to their wide range of biological interactions.[1] Many of them exhibit antibacterial, anticonvulsant, anticancer activities and are used to fight infections involving AIDS.[2–4] They are also applied in agriculture as herbicides, fungicides or insecticides.[5,6] Some 1,3,4-oxadiazoles substituted with aryl groups at positions 2 and 5 are of significant interest in polymer and material science because of their electrochemical properties (luminescence).[7–9]

Generally, methods for the synthesis of the 1,3,4-oxadiazole ring could be divided into two groups according to the starting material. The first group makes use of acid hydrazides bearing in their structure four atoms O–C–N–N essential for the construction of such a ring. They react with synthons introducing to that structure another carbon atom. The most popular synthons here are aromatic aldehydes,[10] carboxylic acids[4] and orthoesters.[11] The second group of methods comprises the reactions of diacylhydrazines, which already contain in their structure all atoms O–C–N–N–C necessary to form a 1,3,4-oxadiazole ring. Such substituted hydrazines are usually treated with a range of cyclodehydrating agents just to mention: polyphosphoric acid,[12] phosphorus oxychloride,[13] thionyl chloride,[14] boron trifluoride diethyl etherate[15] or Burgess reagent.[16]

Our earlier studies on the reactions of α-hydroxyacid hydrazides with triethyl orthoesters in glacial acetic acid led us to a mixture of 1,3,4-oxadiazole and 1,3,4-oxadiazin-5(6*H*)-one derivatives.[17] The formation of the latter six-membered compounds was the result of the presence of a highly reactive hydroxy group in hydrazide. It was interesting if other hydrazides containing the substituents different to the hydroxy at the α-position would undergo the 1,3,4-oxadiazole formation. To the best of our knowledge there is only one mention on the reaction of phenylglycine and orthoesters in dimethylformamide medium leading to 1,2,4-triazine-6(5*H*)-one derivatives.[18] We decided to protect the highly reactive amino group in the α-amino substrate to avoid the further formation of such six-membered products and carry out the reactions with triethyl orthoesters in order to obtain desired five-membered heterocycles.

2. Results and discussion

The two enantiomers of phenylglycine were converted into the corresponding methyl esters **2** and then protected with the use of two typical protective agents: acetic acid anhydride (*path a*) and di-*tert*-butyl pyrocarbonate (*path b*). The protected esters **3** were treated with hydrazine hydrate to give α-*N*-protected hydrazides **4a–d** (Scheme 1). They were subjected to heating with the excess of triethyl orthoesters (R^2=H, Me, Et, Ph) yielding the acyclic derivatives of 1-(alkanecarbonyl)-2-ethoxymethylenehydrazines **5** as the only products.[19] The introduction of an acidic solvent (glacial acetic acid) to the reaction mixture resulted in changing the course

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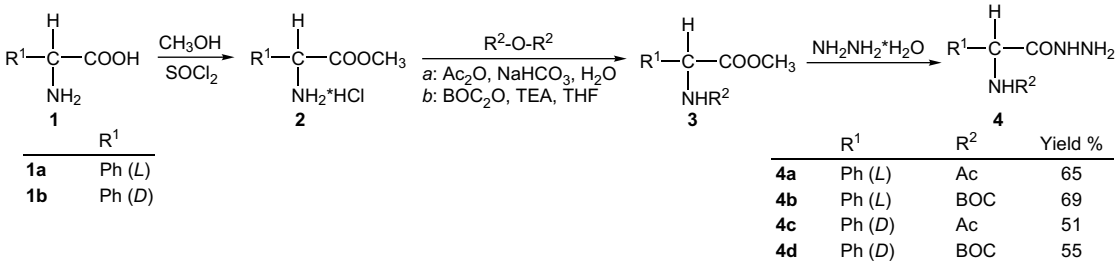
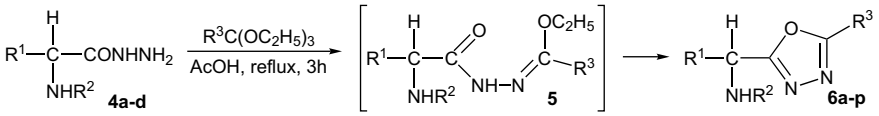


	R^1
1a	Ph (*L*)
1b	Ph (*D*)

	R^1	R^2	Yield %
4a	Ph (*L*)	Ac	65
4b	Ph (*L*)	BOC	69
4c	Ph (*D*)	Ac	51
4d	Ph (*D*)	BOC	55

Scheme 1.



Scheme 2.

of reaction and afforded 2,5-disubstituted-1,3,4-oxadiazoles **6a–p** (Scheme 2).

Similar to the previous groups of 1,3,4-oxadiazoles derived from α-hydroxyacid hydrazides,[17] the highest yields were obtained in those cases where R^2 was phenyl (72–80%). The rest of 1,3,4-oxadiazoles with hydrogen and electron donating substituents at the 5-position were prepared in slightly lower yields (38–74%) (Table 1).

The measurements of the optical rotation for four series of 1,3,4-oxadiazoles derived from enantiomeric substrates: the *N*-acyl (*N*-Ac) and *N*-*tert*-butoxycarbonyl (*N*-BOC) protected L-(+)- and D-(−)-phenylglycine hydrazides **4a–d** showed that they are formed as racemic mixtures. These observations were really surprising because the asymmetric carbon atom is not involved in the formation of 1,3,4-oxadiazole **6**. Analyzing the mechanism of the reaction we assumed that the intermediate 1-(alkanecarbonyl)-2-ethoxymethylenehydrazine **A** played the essential role in the building of the heterocyclic product. Hydrazine **A** may occur in polar solvent in other tautomeric forms: hydroxyhydrazone **B** or enol **C**, where the second methylene carbon atom appears. It is substituted with the hydroxy group that attacks *N*-ethoxymethylene carbon atom yielding 1,3,4-oxadiazole arrangement. Due to racemization we came to conclusion that the enol form **C** is the one that dominates in polar solvent and plays the essential role in the formation of 1,3,4-oxadiazole. The optical activity of carbon atom of the phenylmethyl part disappears in such a structure. It is restored again after the intramolecular substitution of ethoxy group and the following aromatization (double bond and proton migration) yielding the mixture of enantiomers (Scheme 3).

If the nature of solvent is responsible for the racemization, replacing the polar solvent by non-polar one should prevent that phenomenon. We renewed our experiments and heated hydrazides **4b**,**d** with triethyl orthoesters in benzene in the presence of glacial acetic acid. In these cases we obtained pure enantiomers of the appropriate *N*-protected 2-aminomethyl-1,3,4-oxadiazoles. The acetic acid present in the reaction mixture seems not to be responsible for the racemization of final products. The parallel investigation on the 1-(alkanecarbonyl)-2-ethoxymethylenehydrazines **5** obtained with the use of only triethyl orthoesters revealed that even these intermediates exist as racemic mixtures.[19] Thus, the racemization process is caused by polar triethyl orthoester.

The structure of one of the *N*-protected 1,3,4-oxadiazoles was confirmed by X-ray analysis. ORTEP drawing of *N*-[1-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]acetamide **6d** is shown in Figure 1.

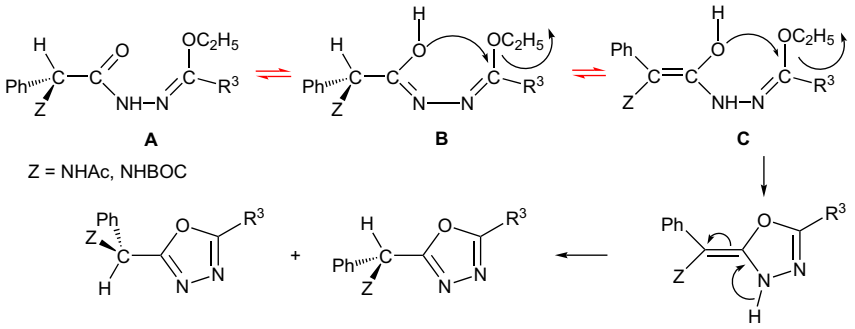
The analysis of the racemic mixture **6d** revealed that the asymmetric part of the unit cell contains two independent molecules **D** and **E** in the same *S* configuration, which means that it crystallizes as a racemic conglomerate. The torsion angle O1n–C2n–C21n–C31n (n=a and b) of −69.3(3)° in molecule **D** and −168.5(2)° in molecule **E** shows that these molecules differ in the conformation. Due to statistical disorder the phenyl ring at position 5 in 1,3,4-oxadiazole ring adopts two different positions with respect to this ring. These positions are described by torsion angles O1a–C5a–C51a–C52c of −8.6(6)° and O1a–C5a–C51a–C52d of 29.9(6)° in molecule **D** and O1b–C5b–C51b–C52e of 13.2(6)° and O1b–C5b–C51b–C52f of −25.0(6)° in molecule **E**.

The last stage of our work was the cleavage reactions of the 1,3,4-oxadiazoles bearing the protected amino groups. According to literature, the *tert*-butoxycarbonyl group (BOC) is usually removed from the *N*-BOC containing compounds with the use of wide range of acidic agents such as hydrochloride in dry ethyl acetate,[20] polyphosphoric acid,[21] boron trifluoride diethyl etherate[22] or trifluoroacetic acid.[23] The deprotection could be also carried out under neutral conditions via thermal decomposition,[24]

Table 1
Characteristics of 2-(1-phenyl-1-*N*-protected-aminomethyl)-1,3,4-oxadiazoles **6a–p** derived from two enantiomeric *N*-protected phenylglycine hydrazides **4a–d**

Compound	R^1	R^2	R^3	Yield %	$[\alpha]_D^{20a,c}$	$[\alpha]_D^{20b,c}$
6a	Ph (L)	Ac	H	51	+0.3	—
6b	Ph (L)	Ac	CH_3	74	+0.4	—
6c	Ph (L)	Ac	C_2H_5	72	0.0	—
6d	Ph (L)	Ac	Ph	80	+0.2	—
6e	Ph (L)	BOC	H	45	+3.2	+86.0
6f	Ph (L)	BOC	CH_3	65	+1.1	+55.2
6g	Ph (L)	BOC	C_2H_5	66	+3.0	+56.4
6h	Ph (L)	BOC	Ph	80	+1.0	+26.0
6i	Ph (D)	Ac	H	59	−0.5	—
6j	Ph (D)	Ac	CH_3	62	0.0	—
6k	Ph (D)	Ac	C_2H_5	65	0.0	—
6l	Ph (D)	Ac	Ph	72	−1.8	—
6m	Ph (D)	BOC	H	38	−8.2	−90.2
6n	Ph (D)	BOC	CH_3	48	−4.0	−54.0
6o	Ph (D)	BOC	C_2H_5	56	−1.0	−55.8
6p	Ph (D)	BOC	Ph	74	−4.0	−25.6

[a] The reaction was conducted in excess of orthoester.
[b] The reaction was conducted in benzene.
[c] Optical rotations for compounds **6e–h**, **6m–p** were measured in chloroform (*c* 1%) and for compounds **6a–d**, **6i–l** in methanol (*c* 1%).



Scheme 3.

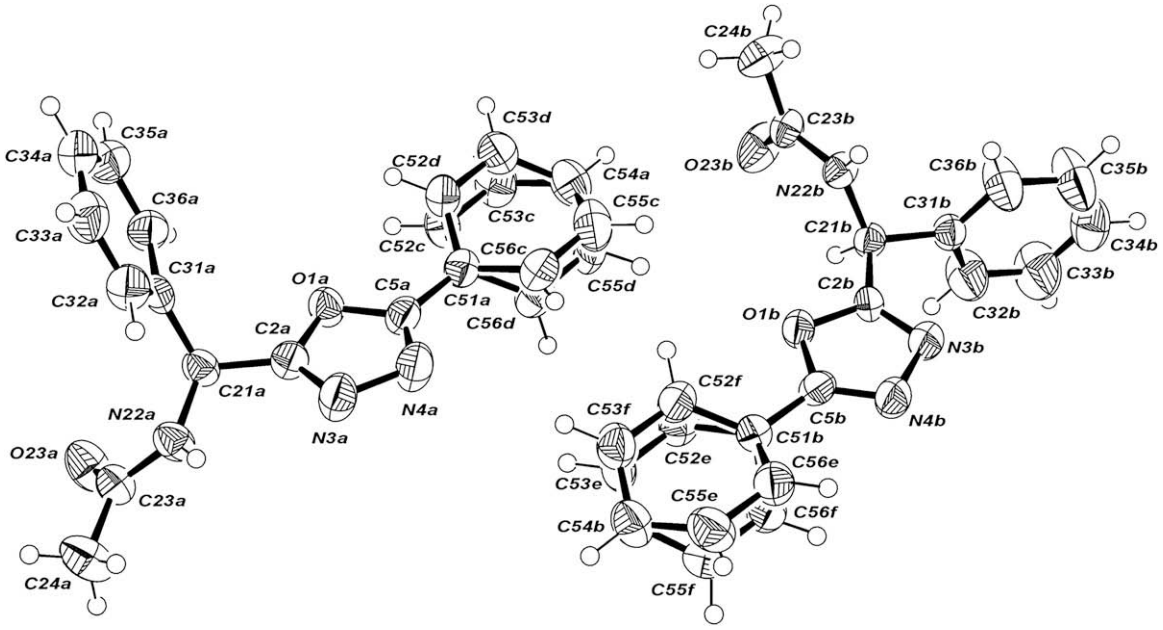
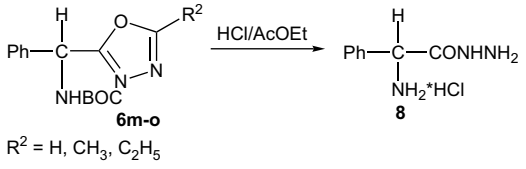


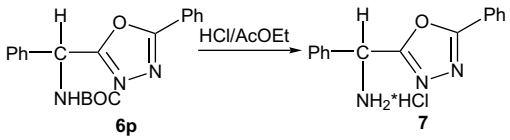
Figure 1. ORTEP drawing of **6d** with numbering of non-H atoms.

employing ceric ammonium nitrate (CAN)[25] or trimethylsilyl trifluoromethanesulfonate (TMS-OTf).[26] Since 1,3,4-oxadiazole ring is acid-sensitive, the number of mild deprotecting agents is rather limited. Nevertheless, we subjected one series of *N*-BOC-protected 1,3,4-oxadiazoles **6m**–**p** to the treatment of hydrochloride in dry ethyl acetate. It appeared that 1,3,4-oxadiazoles substituted at position 5 with H or alkyl groups (R^2=CH_3, C_2H_5) decomposed to deprotected hydrazide **7** (Scheme 4).



Scheme 4.

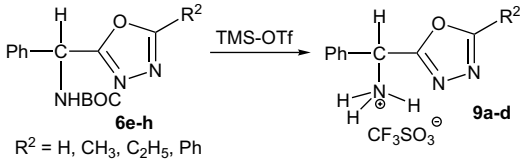
However, when it was substituted with phenyl group, the cleavage of the BOC group was successfully completed and the highly stable heteroaromatic ring was not destructed (**8**, Scheme 5).



Scheme 5.

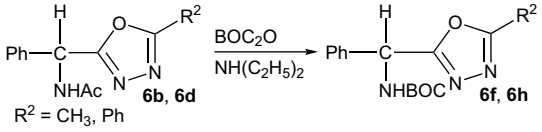
Searching for the versatile deprotecting agent we also conducted the thermal decomposition of *N*-BOC-protected 1,3,4-oxadiazoles and the reactions with CAN unfortunately, without satisfactory results. Finally, the treatment of **6e**–**h** with the excess of trimethylsilyl trifluoromethanesulfonate in dry dichloromethane afforded the *N*-deprotected derivatives **9a**–**d** with untouched 1,3,4-oxadiazole ring (Scheme 6).

More problematic is the cleavage of acetyl group from *N*-Ac-protected 1,3,4-oxadiazoles. The typical method of the deprotection, the acidic hydrolysis, could not be applied here because the heterocyclic ring open easily even at room temperature. Due to this fact, we decided to apply an indirect procedure where *N*-Ac-protected 1,3,4-oxadiazoles **6b**,**d** were treated with di-*tert*-butyl



Scheme 6.

pyrocarbonate and diethylamine yielding the appropriate *N*-BOC-protected 1,3,4-oxadiazoles **6f**,**h** (Scheme 7).



Scheme 7.

Finally, they could be cleaved to 1,3,4-oxadiazoles possessing free aminomethyl group with the use of previously described method involving TMS-OTf.

3. Conclusions

In summary, α-aminoacid hydrazides bearing the protected α-amino group appeared to be useful starting materials in the synthesis of 2-aminomethyl-1,3,4-oxadiazoles. The cleavage of the *tert*-butoxycarbonyl group from *N*-BOC-protected 1,3,4-oxadiazoles possessing the phenyl substituent at 5-position can be successfully carried out with the use of typical agent—hydrochloride in dry ethyl acetate. In contrast, trimethylsilyl trifluoromethanesulfonate is the versatile agent and can be applied to *N*-BOC-protected 1,3,4-oxadiazoles with both aryl and alkyl groups. The arrangements with acyl substituent cannot be cleaved directly to 2-aminomethyl-1,3,4-oxadiazoles because of their high acid-sensitivity. To avoid the ring-opening reaction they should be transformed to their *N*-BOC-protected counterparts and then released with the use of the previously mentioned agents.

4. Experimental

4.1. General

Melting points were measured using an APA II melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were carried out with a VarioEL analyser in PAN Zabrze. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as internal standard. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using benzene–ethyl acetate (1:3 v/v) as the mobile phase. Optical rotations were measured on Perkin–Elmer Polarimeter 141 in chloroform (**2a**, **2b**, **3b**, **3d**, **4b**, **4d**, **6e**–**h**, **6m**–**p**) or methanol (**3a**, **3c**, **4a**, **4c**, **6a**–**d**, **6i**–**l**) solutions at the concentration of approx. 1% (D line of sodium light, room temperature).

4.2. Synthesis of phenylglycine methyl ester hydrochlorides 2

The suspension of 5.00 g (33 mmol) of the appropriate phenylglycine (**1a**,**b**) in 25 mL of methanol was cooled down (0 °C) and 6 mL of thionyl chloride was slowly dropped in. It was stirred for 8 h and then concentrated on the rotary evaporator. The white crude product was washed twice with diethyl ether (2×30 mL), filtered off and dried on air.

*4.2.1. L-(+)-Phenylglycine methyl ester hydrochloride (**2a**)*
Yield: 92%, mp 193–195 °C, $[\alpha]_D^{20}$ +120.0 (*c* 1%, $CHCl_3$).

*4.2.2. D-(−)-Phenylglycine methyl ester hydrochloride (**2b**)*[27]
Yield: 94%, mp 191–193 °C, $[\alpha]_D^{20}$ −119.0 (*c* 1%, $CHCl_3$).

4.3. Synthesis of α-*N*-protected phenylglycine methyl esters 3

Path A (Ac_2O): The appropriate phenylglycine methyl ester hydrochloride (**2a**,**b**) (2.00 g, 10 mmol) was dissolved in 20 mL of cold water. Then 2.13 g (25 mmol) of $NaHCO_3$ was added and after the liberation of CO_2, 1 mL (10 mmol) of acetic acid anhydride was injected. The mixture was stirred for about 15 min and cooled down on ice-bath. The precipitate was filtered off, dried on air and crystallized from isopropanol.

Path B (BOC_2O): The appropriate phenylglycine methyl ester hydrochloride (**2a**,**b**) (2.00 g, 10 mmol) was dissolved in 28 mL of THF. The mixture was cooled down and 1.4 mL (10.6 mmol) of triethylamine was introduced and the whole was stirred for about 20 min. Then 3.28 g (15 mmol) of di-*tert*-butyl pyrocarbonate was added and left agitating at room temperature for 24 h. The white precipitate of triethylamine hydrochloride was filtered off and the solution was evaporated on the rotary evaporator. The white crude product was dried in air and crystallized from isopropanol.

*4.3.1. L-(+)-N-Ac-Phenylglycine methyl ester (**3a**)*
Yield: 81%, mp 114–116 °C, $[\alpha]_D^{20}$ +101.5 (*c* 1%, MeOH).

*4.3.2. L-(+)-N-BOC-Phenylglycine methyl ester (**3b**)*[28]
Yield: 90%, mp 113–115 °C, $[\alpha]_D^{20}$ +189.5 (*c* 1%, $CHCl_3$).

*4.3.3. D-(−)-N-Ac-Phenylglycine methyl ester (**3c**)*[29]
Yield: 86%, mp 115–117 °C, $[\alpha]_D^{20}$ −100.9 (*c* 1%, MeOH).

*4.3.4. D-(−)-N-BOC-Phenylglycine methyl ester (**3d**)*[30]
Yield: 79%, mp 102–104 °C, $[\alpha]_D^{20}$ −187.8 (*c* 1%, $CHCl_3$).

4.4. Synthesis of α-*N*-protected phenylglycine hydrazides 4

The appropriate α-*N*-protected phenylglycine methyl ester (**3a**–**d**) (1.00 g, 3.7 mmol) was dissolved in 18.0 mL of methanol and then 0.6 mL of 98% hydrazine hydrate (12 mmol) was dropped in. It was stirred for 24 h and concentrated under reduced pressure. The oily residue was crystallized by trituration with 10.0 mL of hexane. The crude product was filtered off and recrystallized from a mixture of hexane–methanol (2:3, v/v).

*4.4.1. L-(+)-N-Ac-Phenylglycine hydrazide (**4a**)*
Yield: 85%, mp 210–212 °C, $[\alpha]_D^{20}$ +95.2 (*c* 1%, MeOH), R_f 0.06 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.95; H, 6.33; N, 20.26. Found: C, 58.06; H, 6.36; N, 20.31%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 13.23 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.89 (3H, s, CH_3), 4.28 (2H, s, NH_2), 5.44 (1H, d, *J* 8.7 Hz, CH), 7.26–7.43 (5H, m, Ph), 8.65 (1H, d, *J* 8.7 Hz, NHAc), 9.57 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.43 (CH_3), 54.80 (CH), 127.11, 127.49, 128.27, 139.09 (Ph), 169.02 (CO_{Ac}), 169.36 ($CONHNH_2$).

*4.4.2. L-(+)-N-BOC-Phenylglycine hydrazide (**4b**)*
Yield: 66%, mp 105–107 °C, $[\alpha]_D^{20}$ +105.3 (*c* 1%, $CHCl_3$), R_f 0.15 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 58.85; H, 7.23; N, 15.83. Found: C, 58.80; H, 7.21; N, 15.85%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 14.65 $cm^{-1}\,M^{-1}$), 257 (0.63). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (9H, s, $(CH_3)_3$), 3.68 (2H, s, NH_2), 5.28

(1H, d, *J* 7.2 Hz, CH), 5.99 (1H, d, *J* 7.2 Hz, NHBOC), 7.30–7.38 (5H, m, Ph), 8.25 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.26 ($(CH_3)_3$), 56.99 (CH), 80.33 ($C(CH_3)_3$), 126.97, 128.34, 128.89, 137.64 (Ph), 155.23 (CO_{BOC}), 171.20 ($CONHNH_2$).

*4.4.3. D-(−)-N-Ac-Phenylglycine hydrazide (**4c**)*

Yield: 90%, mp 196–198 °C, $[\alpha]_D^{20}$ −93.6 (*c* 1%, MeOH), R_f 0.05 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.95; H, 6.33; N, 20.26. Found: C, 57.99; H, 6.28; N, 20.21%.) λ_{max} (MeOH): 205 nm ($\varepsilon\cdot10^{-3}$ 17.43 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.89 (3H, s, CH_3), 4.27 (2H, s, NH_2), 5.44 (1H, d, *J* 8.4 Hz, CH), 7.26–7.42 (5H, m, Ph), 8.63 (1H, d, *J* 8.4 Hz, NHAc), 9.54 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.95 (CH_3), 55.25 (CH), 127.58, 127.94, 128.73, 139.59 (Ph), 169.45 (CO_{Ac}), 169.83 ($CONHNH_2$).

*4.4.4. D-(−)-N-BOC-Phenylglycine hydrazide (**4d**)*

Yield: 73%, mp 118–121 °C, $[\alpha]_D^{20}$ −101.7 (*c* 1%, $CHCl_3$), R_f 0.14 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 58.85; H, 7.23; N, 15.83. Found: C, 58.77; H, 7.26; N, 15.89%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 13.10 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (9H, s, $C(CH_3)_3$), 3.82 (2H, s, NH_2), 5.29 (1H, d, *J* 7.5 Hz, CH), 6.04 (1H, d, *J* 7.5 Hz, NHBOC), 7.27–7.37 (5H, m, Ph), 8.23 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.27 ($(CH_3)_3$), 56.92 (CH), 80.32 ($C(CH_3)_3$), 126.92, 128.30, 128.86, 137.66 (Ph), 155.24 (CO_{BOC}), 171.21 ($CONHNH_2$).

4.5. General procedure for the preparation of *N*-protected 2-(1-amino-1-phenylmethyl)-1,3,4-oxadiazoles (6a–p)

Racemates: The starting *N*-protected phenylglycine hydrazide (**4a**–**d**) (0.01 mol) was added to a mixture of the appropriate triethyl orthoester (0.05 mol) and 10.0 mL of glacial AcOH. It was kept under reflux for about 3 h. After cooling the excessive orthoester and AcOH were evaporated under reduced pressure. The crude white products (**6a**–**p**) were subjected to the column chromatography (silica gel, eluent: benzene–AcOEt 1:3 or 1:5 mixtures) or were crystallized from benzene–hexane mixtures.

Enantiomers: The starting *N*-BOC-phenylglycine hydrazide (**4b**,**d**) (0.01 mol) was added to the mixture of the appropriate triethyl orthoester (0.05 mol), 100.0 mL of benzene and 10.0 mL of glacial AcOH. It was kept under reflux for about 1–2 h (TLC). After cooling the solution was concentrated on the rotary evaporator and left for crystallization. Pure products (**6e**–**h**, **6m**–**p**) were recrystallized from benzene–hexane mixtures.

*4.5.1. 2-(1-N-Acylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6a**,**i**)*

Yield: 59%, mp 120–121 °C, R_f 0.07 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.83; H, 5.10; N, 19.34. Found: C, 60.58; H, 5.14; N, 19.29%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 16.70 $cm^{-1}\,M^{-1}$), 257 (0.56). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.95 (3H, s, CH_3), 6.40 (1H, d, *J* 7.8 Hz, CH), 7.36–7.42 (5H, m, Ph), 9.18 (1H, d, *J* 7.8 Hz, NH), 9.23 (1H, s, H-C5). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.29 (CH_3), 48.75 (CH), 127.59, 128.41, 128.79, 136.76 (Ph), 154.85 (C5), 165.60 (C2), 169.21 (CO).

*4.5.2. 5-Methyl-2-(1-N-acylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6b**,**j**)*

Yield: 62%, mp 112–113 °C, R_f 0.13 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.12; H, 5.70; N, 18.09%.) λ_{max} (MeOH): 205 nm ($\varepsilon\cdot10^{-3}$ 17.27 $cm^{-1}\,M^{-1}$), 251 (0.54). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.90 (3H, s, CH_3), 2.47 (3H, s, CH_3-C5), 6.30 (1H, d, *J* 8.1 Hz, CH), 7.33–7.40 (5H, m, Ph), 9.19 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.54 (CH_3-C5), 22.32 (CH_3), 48.72 (CH), 127.57, 128.33, 128.75, 136.92 (Ph), 164.23 (C5), 165.71 (C2), 169.16 (CO).

*4.5.3. 5-Ethyl-2-(1-N-acylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6c**,**k**)*

Yield: 65%, mp 89–91 °C, R_f 0.18 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.49; H, 6.18; N, 17.23%.) λ_{max} (MeOH): 201 nm ($\varepsilon\cdot10^{-3}$ 49.27 $cm^{-1}\,M^{-1}$), 261 (1.45). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (3H, t, *J* 7.5 Hz, CH_3-C5), 1.94 (3H, s, CH_3), 2.83 (2H, q, *J* 7.5 Hz, CH_2-C5), 6.33 (1H, d, *J* 8.1 Hz, CH), 7.37–7.41 (5H, m, Ph), 9.15 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.34 (CH_3-C5), 18.29 (CH_2-C5), 22.29 (CH_3), 48.73 (CH), 127.52, 128.31, 128.74, 136.93 (Ph), 165.59 (C2), 168.03 (C5), 169.09 (CO).

*4.5.4. 2-(1-N-Acylamino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**6d**,**l**)*

Yield: 82%, mp 167–168 °C, R_f 0.27 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.56; H, 5.18; N, 14.41%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 27.97 $cm^{-1}\,M^{-1}$), 252 (17.60). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.97 (3H, s, CH_3), 6.44 (1H, d, *J* 8.1 Hz, CH), 7.35–7.96 (10H, m, 2×Ph), 9.29 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.34 (CH_3), 48.96 (CH), 123.13, 126.57, 127.64, 128.39, 128.79, 129.47, 132.14, 136.81 (2×Ph), 164.37 (C5), 165.93 (C2), 169.31 (CO).

*4.5.5. L-(+)-2-(1-N-tert-Butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6e**)*

Yield: 45%, mp 113–115 °C, $[\alpha]_D^{20}$ +86.0 (*c* 1%, $CHCl_3$), R_f 0.51 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.10; H, 6.18; N, 15.27. Found: C, 60.16; H, 6.24; N, 15.35%.) λ_{max} (MeOH): 202 nm ($\varepsilon\cdot10^{-3}$ 12.31 $cm^{-1}\,M^{-1}$), 257 (1.53). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (9H, s, $(CH_3)_3$), 6.14 (1H, d, *J* 8.1 Hz, CH), 7.32–7.45 (5H, m, Ph), 8.31 (1H, d, *J* 8.1 Hz, NH), 9.20 (1H, s, H-C5). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.09 ($(CH_3)_3$), 50.44 (CH), 78.96 ($C(CH_3)_3$), 127.56, 128.22, 128.55, 137.00 (Ph), 154.77 (CO), 156.08 (C5), 165.74 (C2).

*4.5.6. L-(+)-5-Methyl-2-(1-N-tert-butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6f**)*

Yield: 65%, mp 98–100 °C, $[\alpha]_D^{20}$ +55.2 (*c* 1%, $CHCl_3$), R_f 0.52 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.28; H, 6.57; N, 14.53. Found: C, 62.12; H, 6.50; N, 14.45%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 15.94 $cm^{-1}\,M^{-1}$), 257 (1.11). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (9H, s, $(CH_3)_3$), 2.44 (3H, s, CH_3-C5), 6.03 (1H, d, *J* 8.1 Hz, CH), 7.32–7.43 (5H, m, Ph), 8.25 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.55 (CH_3-C5), 28.19 ($(CH_3)_3$), 50.58 (CH), 79.00 ($C(CH_3)_3$), 127.62, 128.25, 128.63, 137.21 (Ph), 155.01 (CO), 164.25 (C5), 165.93 (C2).

*4.5.7. L-(+)-5-Ethyl-2-(1-N-tert-butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6g**)*

Yield: 66%, mp 123–125 °C, $[\alpha]_D^{20}$ +56.4 (*c* 1%, $CHCl_3$), R_f 0.52 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.37; H, 6.97; N, 13.86. Found: C, 62.35; H, 7.10; N, 13.56%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 49.27 $cm^{-1}\,M^{-1}$), 257 (1.55). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (3H, t, *J* 8.1 Hz, CH_3-C5), 1.38 (9H, s, $(CH_3)_3$), 2.81 (2H, q, *J* 8.1 Hz, CH_2-C5), 6.03 (1H, d, *J* 8.1 Hz, CH), 7.31–7.41 (5H, m, Ph), 8.24 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.45 (CH_3-C5), 18.35 (CH_2-C5), 28.19 ($(CH_3)_3$), 50.63 (CH), 78.99 ($C(CH_3)_3$), 127.62, 128.24, 128.63, 137.22 (Ph), 155.03 (CO), 165.82 (C2), 168.10 (C5).

*4.5.8. L-(+)-2-(1-N-tert-Butoxycarbonylamino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**6h**)*

Yield: 80%, mp 131–133 °C, $[\alpha]_D^{20}$ +26.0 (*c* 1%, $CHCl_3$), R_f 0.52 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.37; H, 5.98; N, 11.97. Found: C, 68.19; H, 6.11; N, 11.85%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 24.98 $cm^{-1}\,M^{-1}$), 252 (18.00). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (9H, s, $(CH_3)_3$), 6.19 (1H, d, *J* 8.1 Hz, CH),

7.34–7.95 (10H, m, 2×Ph), 8.38 (1H, s, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.10 ($(CH_3)_3$), 50.63 (CH), 79.03 ($C(CH_3)_3$), 123.14, 126.48, 127.55, 128.25, 128.62, 129.45, 132.10, 137.06 (2×Ph), 155.00 (CO), 164.33 (C5), 165.99 (C2).

*4.5.9. D-(−)-2-(1-N-tert-Butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6m**)*

Yield: 38%, mp 113–114 °C, $[\alpha]_D^{20}$ −90.2 (*c* 1%, $CHCl_3$), R_f 0.52 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.10; H, 6.18; N, 15.27. Found: C, 60.20; H, 6.14; N, 15.32%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 14.80 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (9H, s, $(CH_3)_3$), 6.15 (1H, d, *J* 8.1 Hz, CH), 7.21–7.54 (5H, m, Ph), 8.32 (1H, d, *J* 8.1 Hz, NH), 9.20 (1H, s, H-C5). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.11 ($(CH_3)_3$), 50.46 (CH), 78.99 ($C(CH_3)_3$), 127.60, 128.26, 128.58, 137.26 (Ph), 155.08 (CO), 154.83 (C5), 165.78 (C2).

*4.5.10. D-(−)-5-Methyl-2-(1-N-tert-butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6n**)*

Yield: 48%, mp 100–102 °C, $[\alpha]_D^{20}$ −54.0 (*c* 1%, $CHCl_3$), R_f 0.49 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.28; H, 6.57; N, 14.53. Found: C, 61.97; H, 6.45; N, 14.59%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 14.20 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (9H, s, $(CH_3)_3$), 2.45 (3H, s, CH_3-C5), 6.05 (1H, d, *J* 8.1 Hz, CH), 7.25–7.52 (5H, m, Ph), 8.26 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.49 (CH_3-C5), 28.13 ($(CH_3)_3$), 50.23 (CH), 78.93 ($C(CH_3)_3$), 127.57, 128.20, 128.28, 137.17 (Ph), 155.30 (CO), 164.21 (C5), 165.09 (C2).

*4.5.11. D-(−)-5-Ethyl-2-(1-N-tert-butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazole (**6o**)*

Yield: 56%, mp 124–125 °C, $[\alpha]_D^{20}$ −55.8 (*c* 1%, $CHCl_3$), R_f 0.53 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.37; H, 6.97; N, 13.86. Found: C, 62.29; H, 6.94; N, 13.92%.) λ_{max} (MeOH): 203 nm ($\varepsilon\cdot10^{-3}$ 13.53 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (3H, t, *J* 7.5 Hz, CH_3-C5), 1.38 (9H, s, $(CH_3)_3$), 2.80 (2H, q, *J* 7.5 Hz, CH_2-C5), 6.03 (1H, d, *J* 8.1 Hz, CH), 7.27–7.45 (5H, m, Ph), 8.25 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.45 (CH_3-C5), 18.35 (CH_2-C5), 28.18 ($(CH_3)_3$), 50.64 (CH), 78.99 ($C(CH_3)_3$), 127.56, 128.25, 128.63, 137.23 (Ph), 155.01 (CO), 165.03 (C2), 168.01 (C5).

*4.5.12. D-(−)-2-(1-N-tert-Butoxycarbonylamino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**6p**)*

Yield: 74%, mp 132–133 °C, $[\alpha]_D^{20}$ −25.6 (*c* 1%, $CHCl_3$), R_f 0.60 (benzene–ethyl acetate, 1:3 v/v). (Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.37; H, 5.98; N, 11.97. Found: C, 68.25; H, 6.07; N, 12.03%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 29.10 $cm^{-1}\,M^{-1}$), 251 (20.68). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (9H, s, $(CH_3)_3$), 6.18 (1H, d, *J* 8.1 Hz, CH), 7.21–7.96 (10H, m, 2×Ph), 8.37 (1H, d, *J* 8.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.09 ($(CH_3)_3$), 50.64 (CH), 79.03 ($C(CH_3)_3$), 123.14, 126.49, 127.55, 128.25, 128.62, 129.46, 132.11, 137.06 (2×Ph), 155.01 (CO), 164.33 (C5), 166.00 (C2).

4.6. Reactions of *N*-BOC-protected 1,3,4-oxadiazoles (6m–p) with hydrochloride in dry ethyl acetate

The *N*-BOC-protected 1,3,4-oxadiazole (**6m**–**p**) (3.5 mmol) was dissolved in 50.0 mL of 1 M solution of HCl in dry ethyl acetate. The mixture was agitated at room temperature until the disappearance of the starting material was complete (1–72 h). The precipitate was filtered off and crystallized from isopropanol or hexane–methanol mixture.

*4.6.1. 2-(1-Amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole hydrochloride (**7**)*

Yield: 81%, mp 215–217 °C. (Anal. Calcd for $C_{15}H_{14}N_3OCl$: C, 62.61; H, 4.91; N, 14.60. Found: C, 62.75; H, 4.97; N, 14.68%.) λ_{max} (MeOH): 205 nm ($\varepsilon\cdot10^{-3}$ 34.37 $cm^{-1}\,M^{-1}$), 250 (24.87). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (1H, s, CH), 7.41–8.18 (10H, m, 2×Ph), 9.88 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.29 (CH), 122.69, 126.70, 128.55, 129.07, 129.55, 129.79, 132.52, 132.74 (2×Ph), 162.94 (C2), 164.99 (C5).

*4.6.2. Phenylglycine hydrazide hydrochloride (**8**)*

Yield: 85%, mp 209–211 °C. (Anal. Calcd for $C_8H_{12}N_3OCl$: C, 47.65; H, 6.01; N, 20.83. Found: C, 47.72; H, 5.97; N, 20.76%.) λ_{max} (MeOH): 206 nm ($\varepsilon\cdot10^{-3}$ 14.45 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (2H, br s, NH_2), 5.03 (1H, s, CH), 6.05 (1H, s, NH), 7.57–7.62 (5H, m, Ph), 8.94 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.17 (CH), 128.96, 129.20, 129.94, 133.77 (Ph), 162.86 (CO).

4.7. Reactions of *N*-BOC-protected 1,3,4-oxadiazoles (6e–h) with trimethylsilyl trifluoromethanesulfonate

The *N*-BOC-protected 1,3,4-oxadiazole (**6e**–**h**) (3.5 mmol) was dissolved in 10.0 mL of dry dichloromethane and to such a solution trimethylsilyl trifluoromethanesulfonate (10.5 mmol) in 10 mL dry dichloromethane was added. The mixture was stirred at room temperature until the disappearance of the starting material was complete (1 h). Then it was evaporated on the rotary evaporator and the crude solid was crystallized from isopropanol.

*4.7.1. 1-(1,3,4-Oxadiazol-2-yl)-1-phenylmethylammonium trifluoromethanesulfonate (**9a**)*

Yield: 96%, mp 118–120 °C. (Anal. Calcd for $C_{10}H_{10}N_3O_4F_3S$: C, 36.92; H, 3.10; N, 12.91. Found: C, 37.09; H, 3.01; N, 13.02%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 11.52 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.15 (1H, s, CH), 7.38–7.46 (5H, m, Ph), 9.31 (1H, s, H-C5), 9.32 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.95 (CH), 119.01 (CF_3), 127.76, 128.42, 128.77, 137.21 (Ph), 165.82 (C2), 169.21 (C5).

*4.7.2. 1-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-phenylmethylammonium trifluoromethanesulfonate (**9b**)*

Yield: 95%, mp 148–150 °C. (Anal. Calcd for $C_{11}H_{12}N_3O_4F_3S$: C, 38.98; H, 3.57; N, 12.38. Found: C, 38.77; H, 3.61; N, 12.43%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 16.32 $cm^{-1}\,M^{-1}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.83 (3H, t, *J* 8.1 Hz, CH_3-C5), 6.10 (1H, s, CH), 7.43–7.51 (5H, m, Ph), 9.30 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.48 (CH_3-C5), 50.02 (CH), 118.21 (CF_3), 128.01, 128.71, 128.89, 133.17 (Ph), 164.78 (C2), 167.79 (C5).

*4.7.3. 1-(5-Ethyl-1,3,4-oxadiazol-2-yl)-1-phenylmethylammonium trifluoromethanesulfonate (**9c**)*

Yield: 94%, mp 176–178 °C. (Anal. Calcd for $C_{12}H_{14}N_3O_4F_3S$: C, 40.79; H, 4.00; N, 11.89. Found: C, 40.86; H, 4.05; N, 11.97%.) λ_{max} (MeOH): 205 nm ($\varepsilon\cdot10^{-3}$ 13.24 $cm^{-1}\,M^{-1}$), 240 (3.50). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (3H, t, *J* 8.1 Hz, CH_3-C5), 2.86 (2H, q, *J* 8.1 Hz, CH_2-C5), 6.20 (1H, s, CH), 7.44–7.53 (5H, m, Ph), 9.30 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.30 (CH_3-C5), 18.30 (CH_2-C5), 49.60 (CH), 118.85 (CF_3), 127.99, 128.36, 128.91, 132.60 (Ph), 164.72 (C2), 169.10 (C5).

*4.7.4. 1-(5-Phenyl-1,3,4-oxadiazol-2-yl)-1-phenylmethylammonium trifluoromethanesulfonate (**9d**)*

Yield: 97%, mp 120–122 °C. (Anal. Calcd for $C_{16}H_{14}N_3O_4F_3S$: C, 47.88; H, 3.52; N, 10.46. Found: C, 47.72; H, 3.58; N, 10.51%.) λ_{max} (MeOH): 204 nm ($\varepsilon\cdot10^{-3}$ 19.62 $cm^{-1}\,M^{-1}$), 249 (11.40). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.24 (1H, s, CH), 7.50–7.98 (10H, m, 2×Ph), 9.40 (3H, br s, NH_3^+). ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.67 (CH), 118.65 (CF_3), 122.65, 126.85, 128.53, 129.41, 129.72, 130.20, 132.53, 136.89 (2×Ph), 164.37 (C5), 165.93 (C2).

4.8. Reactions of *N*-Ac-protected 1,3,4-oxadiazoles (6b,d) with BOC_2O and diethylamine

The mixture of *N*-Ac-protected 1,3,4-oxadiazoles (**6b**,**d**) (3.5 mmol), 5 mL of methanol, diethylamine (7.0 mmol) and BOC_2O anhydride (3.6 mmol) was heated under reflux until the disappearance of the starting material was complete (TLC, 5–10 h). Then it was evaporated on the rotary evaporator and the crude solid was crystallized from benzene–hexane mixture. The reactions gave the appropriate pure *N*-BOC-protected 1,3,4-oxadiazoles: **6f** (yield: 95%, mp 98–101 °C), **6h** (yield: 96%, mp 131–132 °C).

4.9. X-ray crystal structure analysis for 6d

$C_{17}H_{15}N_3O_2$, M=293.32, colourless crystal, 0.50×0.06×0.03 mm, triclinic, space group $P\bar{1}$, a=4.9435(4) Å, b=8.5742(7) Å, c=18.1771(15) Å, α=87.621(2)°, β=82.259(2)°, γ=77.721(2)°, V=745.91(11) Å^3, Z=2, ρ_{calcd}=1.306 g cm^{-3}, μ(Mo Kα)=0.088 mm^{-1}, λ=0.71073 Å, ω scans, multi-scan absorption correction, T_{min}/T_{max} 0.9573/0.9974, range for data collection θ=2.26–27.9°, index ranges (h, k, l) −6/6, −11/11, −23/23, 16,007 measured reflections, 3580 independent reflections (R_{int}=0.0323) and 2693 observed reflections [$I>2\sigma(I)$], full-matrix least-squares on F^2 refinement method, R=0.0393, $wR(F^2)$=0.1026, goodness-of-fit on F^2 S=1.045, data/restraints/parameters 3580/3/467, extinction coefficient 0.037(7), largest diff. peak and hole +0.160/−0.123 e Å^{-3}.

The needle-shaped crystals of **6d** suitable for X-ray diffraction analysis were grown by slow evaporation of an ethanol solution. X-ray data were collected on the Bruker SMART APEX II CCD diffractometer at room temperature. The structure was solved by direct methods using SIR92[31] and refined by full-matrix least-squares with SHELXL97.[32] The final residual electron-density map showed that the C52, C53, C55 and C56 atoms in phenyl rings of the both molecules in the asymmetric part of unit cell are disordered over two sites. The occupancy factors for the split carbon atoms were fixed at 0.5 in the last cycles of refinement. The H atoms were positioned geometrically and treated as riding on their parent C and N atoms with C–H distances of 0.93 Å (aromatic), 0.96 Å (CH_3) and 0.98 Å (CH) and N–H distances of 0.86 Å. All H atoms were refined with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. As there are no significant anomalous scatterers in the molecule, the Flack parameter[33] could not be used to determine the absolute structure. Therefore 3547 Friedel equivalents were merged before the final refinement and the enantiomer was assigned by reference to an unchanging chiral centre in the synthetic procedure. Molecular graphic was prepared using ORTEP3 for Windows.[34] PARST[35] and PLATON[36] were used for geometrical calculations. All calculations were performed using WINGX version 1.64.05 package.[37] CCDC 700769 for **6d** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

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