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Synthesis of trifluoromethylated 2-benzoyl- and 2-aminoimidazoles from ring rearrangement of 1,2,4-oxadiazole derivatives

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Abstract

Fluoroalkylated 2-ylamino-imidazoles have been synthesized by reaction of 3-amino-5-phenyl-1,2,4-oxadiazole with fluorinated β-dicarbonyl compounds and subsequent base-induced Boulton–Katritzky Rearrangement (BKR) of the isolated β-enaminocarbonyl intermediate. Alternatively, one-pot reactions performed in the presence of Montmorillonite K10 favoured the condensation at the 3-amino moiety of the oxadiazole and, in some cases, allowed the direct synthesis of 2-benzoylamino-imidazoles. Hydrolysis of 2-benzoylamino-imidazoles easily yielded fluorinated 2-amino-imidazoles targets.

Keywords: 1,2,4-Oxadiazole; Montmorillonite; Imidazoles; β-Dicarbonyls; β-Enaminoketones; Crystal structure

1. Introduction

The imidazole ring plays a critical role in many aspects of biological structure and function. For example, the imidazole ring of the aminoacid histidine is often found in the active catalytic site of enzymes. Considering the important function of this heterocycle, it is not surprising that many ring-fluorinated imidazoles possess quite interesting biological properties.[1] Moreover, perfluoroalkylated imidazoles have been used as ^{19}F NMR spectroscopic probes for biomimetic studies[2] and intracellular pH determinations,[3] ionic liquids[4] and lightfast optical recording media.[5] In turn, 2-amino-imidazole moieties are present in several biologically active marine alkaloids[6] and this prompted research into efficient and general methodologies for the synthesis of these target molecules.[7]

Nevertheless, despite their potential interest as bioactive molecules, to the best of our knowledge, no fluoroalkylated 2-aminoimidazole has been ever reported. The only example regards trifluoromethylated imidazo[1,2-*a*]benzimidazoles [containing a tertiary amino moiety on the C(2) of the fluorinated imidazole nucleus], which have been recently reported as corticotropin-releasing factor 1 receptor (CRF1R) antagonists for the treatment of depression, anxiety and stress-related disorders.[8]

We therefore decided to synthesize a series of trifluoromethylated imidazole derivatives by following the *Ring-Rearrangement Approach*, which takes advantage of the thermal and photochemical reactivities of suitable heterocyclic synthons and is a very versatile approach to fluorinated heterocycles.[9] In this context, it is worth remarking that the presence of a fluorinated moiety [either as a fluorine atom, as a per(poly)-fluoroalkyl or as a per(poly)fluoroaryl group] can strongly affect such reactivity or the outcome of the reaction with respect to the results obtained with non-fluorinated analogues.[9] In the last decade, we have been revisiting several reactions of the 1,2,4-oxadiazole, a heterocycle, which is very likely to undergo ring rearrangement into the more stable heterocycles, with the aim of synthesizing fluorinated heterocyclic targets.[9] An interesting example of the reactivity of 1,2,4-oxadiazoles is afforded by *N*-(1,2,4-oxadiazol-3-yl)-β-enaminoketones **1**. For these systems, two different rearrangements have been shown

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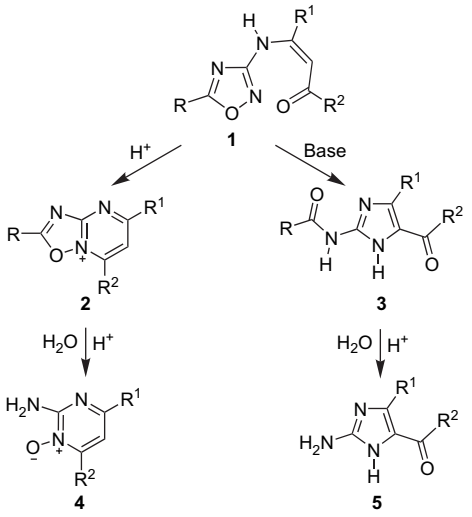
as a function of the experimental conditions (Scheme 1): (i) in acidic media, a four-atom side-chain rearrangement yields 2-amino-pyrimidine-*N*-oxides **4** through a bicyclic cation intermediate **2**;[10a,b] (ii) in the presence of a base, a three-atom side-chain rearrangement is observed, yielding the corresponding 2-(*N*-acylamino)imidazoles **3**[10c,d] in accordance with the general scheme of the Boulton–Katritzky Rearrangement (BKR).[11,12] Subsequent hydrolysis of compounds **3** gives access to 2-amino-imidazoles **5**.



Scheme 1.

In a recent paper,[13] we have reported on the reactivity of 3-amino-5-methyl-1,2,4-oxadiazole with trifluoromethylated diketones under acidic conditions, leading to fluorinated 2-amino-pyrimidine *N*-oxides and 2-hydroxyaminopyrimidines. In this paper, we report the reaction of 3-amino-5-phenyl-1,2,4-oxadiazole **6** with some trifluoromethylated 1,3-dicarbonyl compounds and the base-induced BKR of some trifluoromethylated *N*-(1,2,4-oxadiazol-3-yl)-β-enaminoketones as an attractive synthetic strategy for the synthesis of trifluoromethylated 2-*N*-benzoylamino- and 2-amino-imidazole derivatives.

2. Results and discussion

The reaction of 3-amino-1,2,4-oxadiazole **6** with trifluoromethylated 1,3-diketones **7a**,**b** was initially performed in refluxing toluene in the presence of *p*-toluenesulfonic acid following the conventional procedure used for the synthesis of non-fluorinated 1,2,4-oxadiazol-3-yl-enaminoketones.[13] However, under these conditions, the substrate remained essentially unchanged; moreover, due to the volatility of **7a**,**b** loss of the diketone in the Dean–Stark apparatus was experienced. The reaction was then performed at rt, in petroleum ether and in the presence of Montmorillonite K10 (Mont-K10) as an heterogeneous acid catalyst.[14] Under these conditions, enaminoketone **12a** (80%) was obtained in good yields from **7a** (Scheme 2), while only a small amount of enaminoketone **11b** (5%) was obtained from reaction with **7b**. The structure of compound **12a** was confirmed by X-ray data (see Fig. 1) and is in agreement with a condensation reaction involving the CH_3CO carbonyl, according to a previous report.[13]

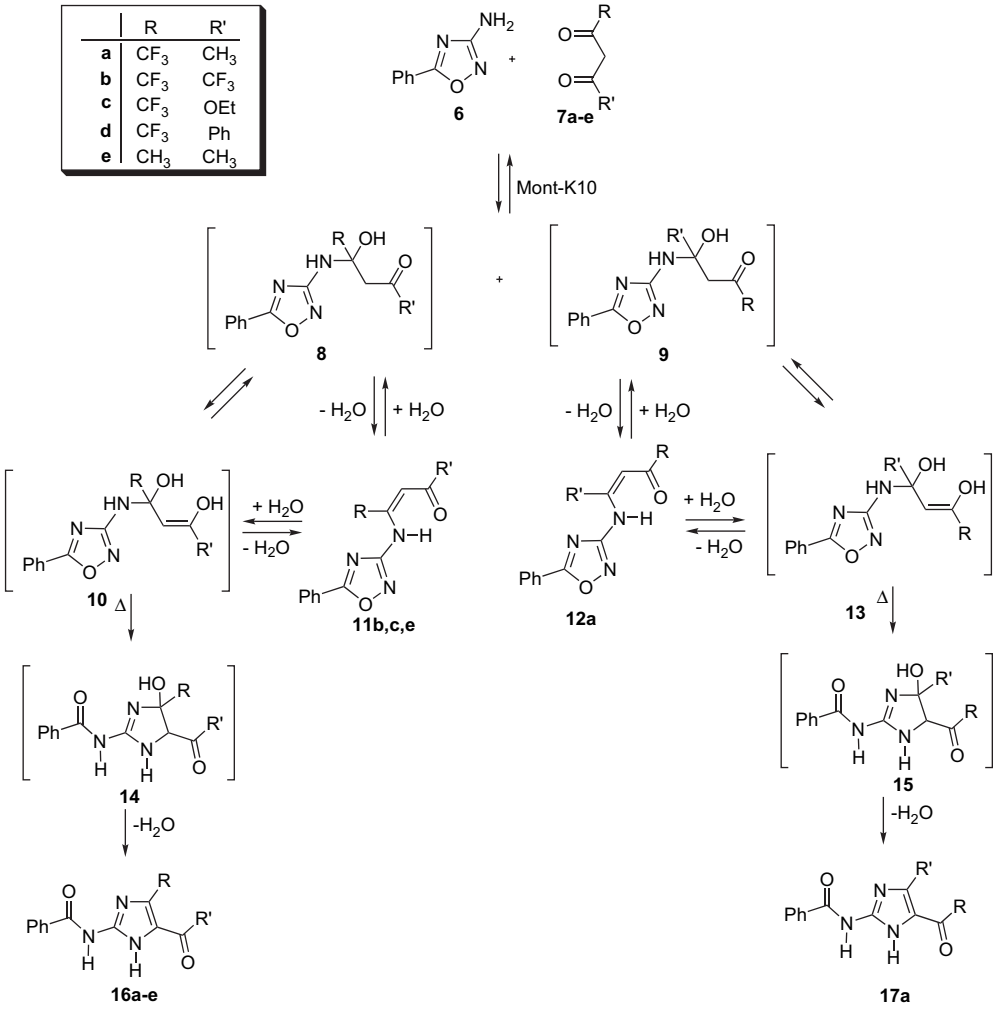
Attempting to improve the yields of **11b**, the reaction was performed at 100 °C in toluene/Mont-K10 in a sealed tube for 6 h. Under these conditions, compound **11b** was obtained in 25% yield (with 73% of recovered starting compound **6**); however, prolonged heating lowered the yield and led to the formation of decomposition products.

These conditions were then adopted as a general procedure for the reaction of amine **6** with fluorinated 1,3-dicarbonyl compounds **7a–d**, as well as for a comparison with the non-fluorinated diketone **7e**. Interestingly, for the reactions of **6** with compounds **7a**,**c**, besides the expected β-enaminocarbonyl compounds **12a** and **11c**, were also isolated 4(5)-trifluoromethyl-2-(*N*-benzoylamino)-imidazoles **16a**,**c** while in the reaction with diketone **7d**, only the imidazole **16d** was obtained (see Table 1). In order to assess the role of the fluorinated group on the observed reactivity, reaction of amine **6** with the non-fluorinated symmetric diketone **7e** was performed, resulting in the formation of enaminoketone **11e** (43%) together with the corresponding imidazole **16e** (15%).

It is important to remark that the regiochemistry of the reaction of amino compound **6** with unsymmetrical diketones might depend on several factors such as: (i) the keto–enolic equilibrium of the diketonic reagent,[15] (ii) the electrophilic character of the two carbonyls on the diketone and (iii) the stability of the carbinolamine intermediate in either its keto (**8** or **9**) or its enol (**10** or **13**) form.[16] These factors, together with the presence of trifluoromethyl groups and a possible involvement of the heterogeneous catalyst used, play an important role in driving the reaction either towards the formation of the enaminoketones (**11** or **12**) or towards the acylimidazole (**16** or **17**). In the latter case, this reaction represents the first example of an acid catalyzed Boulton–Katritzky rearrangement (BKR) involving an NCC side chain. In order to assess whether the imidazoles originate directly from a BKR of the corresponding enaminoketone precursors, a separate experiment has been conducted by reacting compounds **11c**,**e** and **12a** in refluxing toluene in the presence of Montmorillonite K10. In all the cases, ready hydrolysis to amine **6** was observed; moreover, in the case of **11c**, only a small amount of the corresponding imidazole **16c** (15%) was isolated; interestingly, in the reaction of **12a** both imidazole regioisomers **16a** (20%) and **17a** (5%) were formed. These results (the lower yields in imidazole with respect to the one-pot reaction and the formation of the two regioisomers **16a** and **17a**) clearly rule out any role of the enaminoketone as a reaction intermediate in the reaction with Mont-K10.

An intriguing mechanistic hypothesis considers the Montmorillonite activation of the oxadiazole ring towards the nucleophilic attack by the enol moiety of the side chain. Thus the carbinolamine intermediate **10** (or **13**) undergoes an acid catalyzed BKR into imidazoline **14** (or **15**), which can be easily dehydrated to the corresponding aromatic imidazole **16** (or **17**).

In their turn, the β-enaminocarbonyl compounds **11b**,**c** and **12a** were refluxed in DMF and in the presence of an excess of



Scheme 2.

t-BuOK to obtain the corresponding 2-(*N*-benzoylamino)-imidazoles **16b**,**c**, and **17a** (Scheme 3). It is worth noting that this rearrangement allows one to complete the series of imidazole targets considering that imidazoles **16b** and **17a** were not obtained through the Mont-K10 catalyzed one-pot reaction.

The regio-chemical issue for compounds **16a**,**d** and **17a** was unambiguously resolved by means of ^{1}H NMR spectroscopic determination of their reduction products **18a–c**, respectively (Scheme 4).

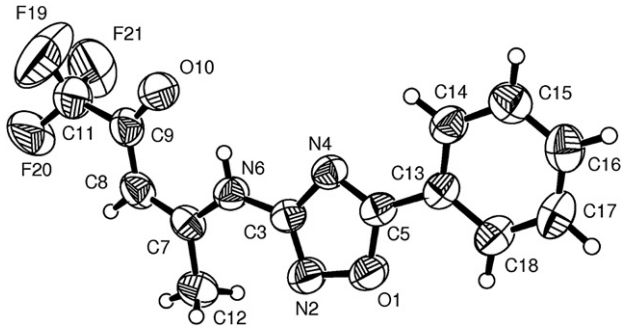


Figure 1. ORTEP drawing of compound **12a**.

Table 1
Product distribution for Montmorillonite K10 catalyzed reaction of oxadiazole **6** with 1,3-dicarbonyls **7a–e** in toluene at 100 °C

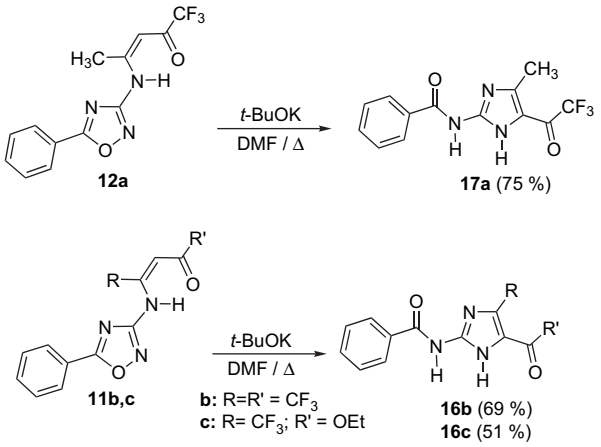
Reagent	Reaction time (h)	Recovered **6** (%)	Yield of **11** (%)	Yield of **12** (%)	Yield of **16** (%)	Yield of **17** (%)
7a	24	5	—	44	29	—
7b	6	73	25	[a]	—	[a]
7c	24	16	57	—	27	—
7d	72	36	—	—	23	—
7e	8	10	43	[a]	15	[a]

[a] For reaction with a symmetrical diketone, product **12** is identical to **11** and product **16** is identical to **17**.

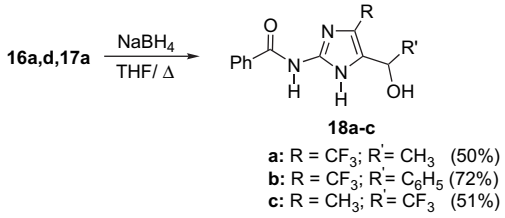
Finally, all the obtained fluorinated 2-benzoylamino-imidazoles **16a–d** and **17a** were easily hydrolyzed, under acidic conditions, to the corresponding trifluoromethylated 2-amino-imidazoles **19a–e** (Scheme 5), whose structure was confirmed by spectroscopic (IR, ^{1}H NMR, HRMS) and X-ray (for representative **19d**, see Fig. 2) data.

3. Conclusions

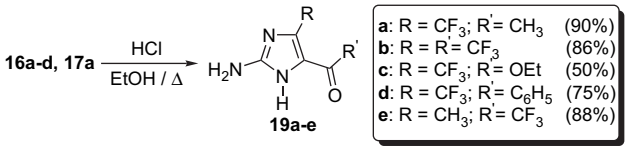
The synthesis of a series of trifluoromethylated 2-benzoylamino-imidazoles, hydrolyzed into their corresponding



Scheme 3.



Scheme 4.



Scheme 5.

2-amino derivatives, was achieved through Boulton–Katritzky rearrangements of 1,2,4-oxadiazoles bearing an NCC side chain. Besides the classic base-promoted BKR of β-enaminocarbonyl compounds in their anionic form, an acid-catalyzed BKR has been pointed out, likely involving the enolic form of a carbinolamine intermediate and a Montmorillonite–oxadiazole complex. In some cases these appear to be two complementary synthetic approaches. For instance, one-pot reactions with the appropriate 1,3-dicarbonyl reagent allowed the isolation of imidazoles **16a**,**d**, whose enaminoketone precursors **11a**,**d** were not accessible.

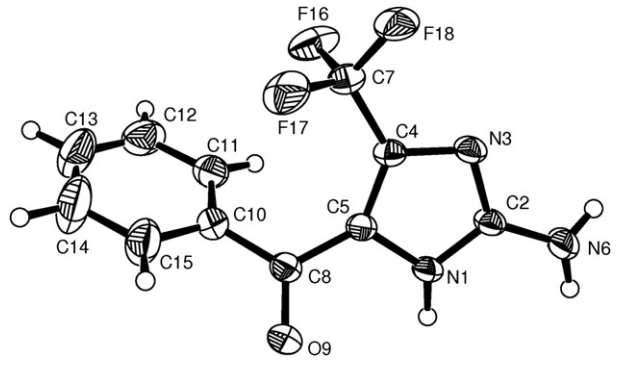


Figure 2. ORTEP drawing of compound **19d**.

4. Experimental

4.1. General methods and materials

Melting points were determined on a REICHART-THERMOVAR hot-stage apparatus. FTIR spectra (Nujol) were determined with a SHIMADZU FTIR-8300 instrument; ^{1}H NMR spectra were recorded on a BRUKER 300 Avance spectrometer and were taken with TMS as an internal standard. Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mesh) and mixtures of light petroleum (fraction boiling in the range of 40–60 °C) and ethyl acetate in varying ratios. Compound **6**[17] was prepared as reported previously. Montmorillonite K10 was purchased and used without further treatment. For X-ray analysis details, see Supplementary data.

4.2. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole *6* with fluorinated β-dicarbonylic compounds *7a–e*: general procedure

Montmorillonite K10 (2 g) was suspended in a stirred solution of **6** (1.5 mmol) in AcOEt. The solvent was eliminated under reduced pressure and the residue suspended in petroleum ether or toluene (10 mL), and was added the appropriate β-dicarbonylic compound **7** (3 mmol). The obtained suspension was allowed to stir at rt using petroleum ether or 100 °C with toluene. The suspension was then filtered and the solid washed with AcOEt several times. The filtrate was dried over Na_2SO_4 and evaporated.

4.2.1. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole *6* with 1,1,1-trifluoro-2,4-pentanedione *7a*

4.2.1.1. Petroleum ether, rt. Chromatography of the residue gave **12a** (79%) and recovered **6** (20%). *1,1,1-Trifluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-4-amino-pent-3-en-2-one* **12a** had mp 127–128 °C (white crystals, from ethanol). FTIR (Nujol) *ν*: 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ*: 2.59 (s, 3H), 5.73 (s, 1H), 7.51–7.67 (m, 3H), 8.09–8.14 (m, 2H), 12.45 (s, 1H, exch. with D_2O). HRMS found: 297.0725; $C_{13}H_{10}F_3N_3O_2$ requires: 297.0725.

4.2.1.2. Toluene, 100 °C. Chromatography of the residue gave **12a** (44%), **16a** (29%) and recovered **6** (5%). *2-N-Benzoyl-amino-4(5)-trifluoromethyl-5(4)-acetyl-imidazole* **16a** had mp 249–251 °C (white crystals, from EtOAc). FTIR (Nujol) *ν*: 3389, 3293, 1667, 1638 cm^{-1}. ^{1}H NMR (DMSO-d_6) *δ*: 2.57 (s, 3H), 7.49–7.71 (m, 3H), 8.08–8.12 (m, 2H), 12.10 (br s, 1H, exch. with D_2O), 12.68 (br s, 1H, exch. with D_2O). HRMS found: 297.0724; $C_{13}H_{10}F_3N_3O_2$ requires: 297.0725.

4.2.2. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole ***6*** *with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione* ***7b***

4.2.2.1. Petroleum ether, rt. Chromatography of the residue gave **11b** (5%) and recovered **6** (94%). *1,1,1,5,5,5-Hexafluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-4-amino-pent-3-en-2-one* **11b** had mp 80–82 °C (white crystals, from petroleum ether). FTIR (Nujol) ν: 1674 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.33 (s, 1H), 7.53–7.70 (m, 3H), 8.11–8.15 (m, 2H), 11.73 (s, 1H, exch. with D_2O). HRMS found: 351.0444; $C_{13}H_7F_6N_3O_2$ requires: 351.0443.

4.2.2.2. Toluene, 100 °C. Chromatography of the residue gave **11b** (25%) and recovered **6** (73%).

4.2.3. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole ***6*** *with ethyl 4,4,4-trifluoroacetoacetate* ***7c***

Chromatography of the residue gave **11c** (57%), **16c** (27%) and recovered **6** (16%). *4,4,4-Trifluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-3-amino-but-2-enoic acid ethyl ester* **11c** had mp 88–90 °C (white crystals, from petroleum ether). FTIR (Nujol) ν: 1676 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.08 (t, 3H, J=8.5 Hz), 3.98 (q, 2H, J=8.5 Hz), 6.13 (s, 1H), 7.65–7.80 (m, 3H), 8.05–8.14 (m, 2H), 10.43 (s, 1H, exch. with D_2O). HRMS found: 327.0831; $C_{14}H_{12}F_3N_3O_3$ requires: 327.0831. *2-N-Benzoylamino-4(5)-trifluoromethyl-5(4)-carboxyethyl-imidazole* **16c** had mp 203–5 °C (white crystals, from ethanol). FTIR (Nujol) ν: 3377, 3317, 1694, 1664 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H, J=8.5 Hz), 4.41 (q, 2H, J=8.5 Hz), 7.51–7.69 (m, 3H), 7.89–7.92 (m, 2H), 9.79 (s, 1H, exch. with D_2O), 11.56 (br s, 1H, exch. with D_2O). HRMS found: 327.0831; $C_{14}H_{12}F_3N_3O_3$ requires: 327.0831.

4.2.4. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole ***6*** *with 4,4,4-trifluoro-1-phenyl-1,3-butanedione* ***7d***

Chromatography of the residue gave **16d** (23%) and recovered **6** (36%). *2-N-Benzoylamino-4(5)-trifluoromethyl-5(4)-benzoyl-imidazole* **16d** had mp 165–167 °C (white crystals, from EtOAc). FTIR (Nujol) ν: 3231, 1657, 1642 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.54–7.73 (m, 6H), 7.81–7.89 (m, 2H), 8.07–8.09 (m, 2H), 12.09 (br s, 1H, exch. with D_2O), 12.92 (br s, 1H, exch. with D_2O). HRMS found: 359.0883; $C_{18}H_{12}F_3N_3O_2$ requires: 359.0882.

4.2.5. Reaction of 3-amino-5-phenyl-1,2,4-oxadiazole ***6*** *with 2,4-pentanedione* ***7e***

Chromatography of the residue gave **11e** (43%, mp 112–113 °C, lit.[10d] 112 °C), **16e** (13%, mp 222–3 °C, lit.[10d] 221 °C) and recovered **6** (10%).

4.3. Rearrangement of N-(1,2,4-oxadiazol-3-yl)-β-enaminocarbonyls ***11b,c*** *and* ***12a****: general procedure*

To a solution of β-enaminocarbonyls (1 mmol) in dry DMF (2 mL), *t*-BuOK (1,2 mmol) was added and the solution refluxed for 2 h. The mixture was diluted with water (100 mL), neutralized with HCl and then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated.

4.3.1. Rearrangement of 1,1,1,5,5,5-hexafluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-4-amino-pent-3-en-2-one ***11b***

Chromatography of the residue gave recovered **11b** (6%), **16b** (69%) and **6** (15%). *2-N-Benzoylamino-4(5)-trifluoromethyl-5(4)-trifluoroacetyl-imidazole* **16b** had mp 41–3 °C (white crystals, from petroleum ether). FTIR (Nujol) ν: 3441, 3413, 1680 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.57–7.70 (m, 3H), 8.10–8.12 (m, 2H), 8.31 (s, 2H, exch. with D_2O, hydrated form), 11.85 (s, 1H, exch. with D_2O), 11.97 (s, 1H, exch. with D_2O). HRMS found: 351.0448; $C_{13}H_7F_6N_3O_2$ requires: 351.0443.

4.3.2. Rearrangement of 4,4,4-trifluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-3-amino-but-2-enoic acid ethyl ester ***11c***

Chromatography of the residue gave **16c** (51%) and **6** (12%).

4.3.3. Rearrangement of 1,1,1-trifluoro-N-(5′-phenyl-1,2,4-oxadiazol-3-yl)-4-amino-pent-3-en-2-one ***12a***

Chromatography of the residue gave **17a** (75%) and recovered **12a** (9%). *2-N-Benzoylamino-4(5)-methyl-5(4)-trifluoroacetyl-imidazole* **17a** had mp 88–90 °C (white crystals, from ethanol/water). FTIR (Nujol) ν: 3303, 1694, 1680 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.64 (s, 3H), 7.55–7.71 (m, 3H), 8.11–8.15 (m, 2H), 11.84 (s, 1H, exch. with D_2O), 13.07 (s, 1H, exch. with D_2O). HRMS found: 297.0725; $C_{13}H_{10}F_3N_3O_2$ requires: 297.0725.

4.4. Reduction of 2-N-benzoylamino-5(4)-acyl-imidazoles ***16a,d*** *and* ***17a****: general procedure*

2-*N*-Benzoylamino-5(4)-acyl-imidazole (1 mmol) was added to a solution of $NaBH_4$ (2 mmol) in THF (10 mL). The solution was refluxed for 2 h and then the solvent was eliminated under reduced pressure. The residue was treated with 1 M HCl (100 mL), refluxed for 30 min, neutralized with NaOH and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated.

4.4.1. Reduction of 2-N-benzoylamino-4(5)-trifluoromethyl-5(4)-acetyl-imidazole ***16a***

Chromatography of the residue gave **18a** (50%) and recovered **16a** (31%). *2-N-Benzoylamino-4(5)-trifluoromethyl-5(4)-(1-hydroxyethyl)-imidazole* **18a** had mp 175–177 °C (white crystals, from EtOAc). FTIR (Nujol) ν: 3371, 3276, 3245, 3165, 1665 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.47 (d, 3H, J=6.6 Hz), 5.03 (dq, 1H, ^1J=6.6 Hz, ^2J=6 Hz), 6.43 (d, 1H, J=6 Hz, exch. with D_2O), 7.57–7.71 (m, 3H), 8.10–8.12 (m, 2H), 11.78 (s, 1H, exch. with D_2O), 12.06 (s, 1H, exch. with D_2O). HRMS found: 299.0883; $C_{13}H_{12}F_3N_3O_2$ requires: 299.0882.

4.4.2. Reduction of 2-N-benzoylamino-4(5)-trifluoromethyl-5(4)-benzoyl-imidazole **16d**

Chromatography of the residue gave **18b** (72%). *2-N-Benzoylamino-4(5)-trifluoromethyl-5(4)-hydroxy(phenyl)methyl-imidazole* **18b** had mp 178–180 °C (white crystals, from water). FTIR (Nujol) ν: 3270, 3225, 3065, 1679 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 5.99 (d, 1H, J=6 Hz, as singlet after exch. with D_2O), 6.36 (d, 1H, J=6 Hz, exch. with D_2O), 7.27–7.39 (m, 5H), 7.51–7.65 (m, 3H), 8.03–8.04 (m, 2H), 11.76 (s, 1H, exch. with D_2O), 12.04 (s, 1H, exch. with D_2O). HRMS found: 361.1039; $C_{18}H_{14}F_3N_3O_2$ requires: 361.1038.

4.4.3. Reduction of 2-N-benzoylamino-4(5)-methyl-5(4)-trifluoroacetyl-imidazole **17a**

Chromatography of the residue gave **18c** (51%) and recovered **17a** (5%). *2-N-Benzoylamino-4(5)-methyl-5(4)-(1-hydroxy-2,2,2-trifluoro-ethyl)-imidazole* **18c** had mp 242–5 °C (white crystals, from EtOAc). FTIR (Nujol) ν: 3310, 3273, 3184, 1654 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.26 (s, 3H), 5.10 (br s, 1H), 6.43 (br s, 1H, exch. with D_2O), 7.53–7.67 (m, 3H), 8.09–8.12 (m, 2H), 11.61–11.73 (br s, 2H, exch. with D_2O). HRMS found: 299.0881; $C_{13}H_{12}F_3N_3O_2$ requires: 299.0882.

4.5. Hydrolysis of 2-N-benzoylamino-imidazoles **16a–d** and **17a**: general procedure

To a solution of 2-*N*-benzoylamino-imidazole (1 mmol) in ethanol (10 mL), hydrochloric acid (0.5 mL) was added and the mixture was refluxed for 24 h. After removal of the solvent, the residue was treated with water, neutralized with solid $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated. Crystallization of the residue from ethanol gave the corresponding 2-amino-imidazole **19**.

4.5.1. 2-Amino-4(5)-trifluoromethyl-5(4)-acetyl-imidazole **19a**

Compound **19a** (90%) had mp 230 °C (dec, white crystals, from ethanol). FTIR (Nujol) ν: 3457, 3273, 3118, 1677 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.40 (s, 3H), 6.15 (s, 2H, exch. with D_2O), 11.63 (s, 1H, exch. with D_2O). HRMS found: 193.0463; $C_6H_6F_3N_3O$ requires: 193.0463.

4.5.2. 2-Amino-4(5)-trifluoromethyl-5(4)-trifluoroacetyl-imidazole **19b**

Compound **19b** (86%) had mp 217–219 °C (crystal, from ethanol). FTIR (Nujol) ν: 3479, 3324, 376, 1697, 1689, 1659 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 6.88 (s, 2H, exch. with D_2O), 12.05 (s, 1H, exch. with D_2O). HRMS found: 247.0177; $C_6H_3F_6N_3O$ requires: 247.0180.

4.5.3. 2-Amino-4(5)-trifluoromethyl-5(4)-carboxyethyl-imidazole **19c**

Chromatography of the residue gave **19c** (50%) and recovered **16c** (22%). Compound **19c** had mp 212–214 °C (white crystals, from ethanol). FTIR (Nujol) ν: 3454, 3295, 3128, 1676, 1640 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.11 (t, 3H, J=7.2 Hz), 4.08 (q, 2H, J=7.2 Hz), 5.83 (s, 2H, exch. with D_2O), 11.50 (s, 1H, exch. with D_2O). HRMS found: 223.0562; $C_7H_8F_3N_3O_2$ requires: 223.0568.

4.5.4. 2-Amino-4(5)-trifluoromethyl-5(4)-benzoyl-imidazole **19d**

Compound **19d** (75%) had mp 218–220 °C (white crystals, from ethanol). FTIR (Nujol) ν: 3461, 3245, 3164, 1652, 1610 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 6.21 (s, 2H, exch. with D_2O), 7.54–7.74 (m, 5H), 11.66 (s, 1H, exch. with D_2O). HRMS found: 255.0622; $C_{11}H_8F_3N_3O$ requires: 255.0619.

4.5.5. 2-Amino-4(5)-methyl-5(4)-trifluoroacetyl-imidazole **19e**

Compound **19e** (88%) had mp 199–201 °C (white crystals, from ethanol). FTIR (Nujol) ν: 3450, 3263, 3055, 1682 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.41 (s, 3H), 6.54 (s, 2H, exch. with D_2O), 11.01 (s, 1H, exch. with D_2O). HRMS found: 193.0464; $C_6H_6F_3N_3O$ requires: 193.0463.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.047.

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