Tetrahedron 64 (2008) 11198–11204

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Effect of the aryl group substituent in the dimerization of 3-arylisoxazoles to *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones induced by LDA

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ARTICLE INFO

Article history:
Received 27 June 2008
Received in revised form 3 September 2008
Accepted 18 September 2008
Available online 30 September 2008

Keywords:
3-Arylisoxazoles
Cage-shaped bis-β-lactams
LDA
EDGs, EWGs
N,*N*-Diisopropylaminobenzonitriles
3-(2-Methylphenyl)isoquinolin-1-amine

ABSTRACT

3-Arylisoxazoles react with LDA in THF at 0 °C affording *syn*-2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones (bis-azetidinones), via stereoselective dimerization of an azetinone anion intermediate. A fragmentation reaction affording arylnitriles may compete with electronic and steric effects of the substituent present in the aryl group being pivotal in determining the outcome of this reaction. An interesting behaviour with LDA of arylnitriles arising from the fragmentation reaction of some 3-arylisoxazoles was also observed. *N*,*N*-Diisopropylaminobenzonitriles were in fact formed (plausibly via a benzyne mechanism) from 3-(4-chlorophenyl)isoxazole and 3-(2-chlorophenyl)isoxazole, whereas 3-(2-methylphenyl)isoquinolin-1-amine was isolated starting from 3-(2-methylphenyl)isoxazole and LDA.

1. Introduction

We have recently reported the synthesis of previously unknown *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones (referred to as bis-azetidinones from now on) by dimerization of 3-arylisoxazoles induced by hindered lithium amides (LDA, LTMP, LHMDS) (Scheme 1).[1]

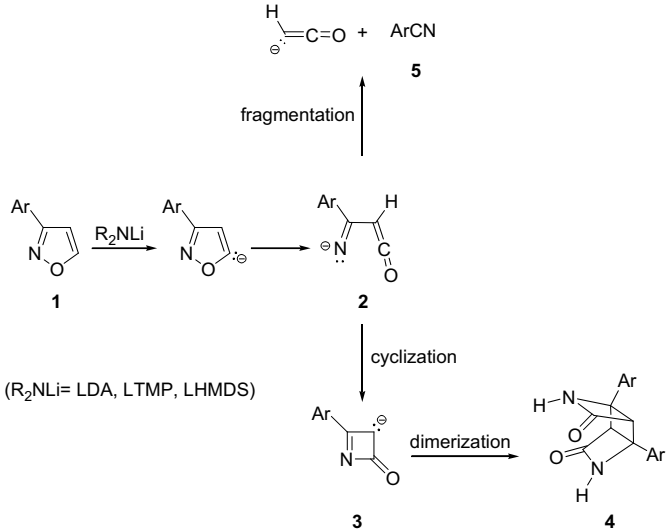
In particular, we investigated the reaction of 3-phenylisoxazole **1** and a small number of 3-(4-substituted-phenyl)isoxazoles observing high yields of the corresponding bis-azetidinones **4**, except for isoxazoles containing electron-donor substituents (EDGs).

The latter compounds, in fact, depending on the magnitude of the electron-donating effect, gave together with bis-azetidinones **4**, also variable amounts of the corresponding arylnitriles **5**, arising from a competitive fragmentation reaction plausibly favoured in the presence of EDGs both for a diminished stability of lithium iminoketenes **2**, and a concomitant increased stability of arylnitriles **5**.

In this paper, we report a more extensive investigation of the substituent effect on such a reaction, including other different substituents and/or different substituted positions of the aryl moiety.

2. Results and discussion

Variously substituted 3-arylisoxazoles **1a–m** were synthesized following the procedure already reported by us,[1,2] and outlined in Scheme 2.



Scheme 1. Reaction of 3-arylisoxazoles with R_2NLi.

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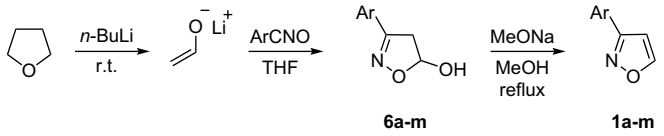
doi:10.1016/j.tet.2008.09.063



Scheme 2. Synthesis of 3-arylisoxazoles (**1a**–**m**) via 3-aryl-5-hydroxy-2-isoxazolines (**6a**–**m**).

In all cases, satisfactory yields of 3-arylisoxazoles **1a**–**m** were obtained, as reported in Table 1.

The synthesized 3-arylisoxazoles **1a**–**m** include a variety of substituents with different electronic effects and/or attached at different positions of the aryl moiety.

All the synthesized compounds (**1a**–**m**) were reacted with LDA under the same previously reported conditions,[1] observing also the same behaviour (see Scheme 1), with relative percentages (%) of the isolated products depending on the features and the position of the substituent.

In some cases (aryl=4-chlorophenyl-, 2-chlorophenyl- and 2-methylphenyl-), variable amounts of additional products generated by further reaction of the initially formed arylnitriles with LDA were also isolated. The obtained results are summarized in Table 2.

Examination of the obtained results allows several comments to be made. First of all, the previously observed trend concerning the favourable effect of electron-withdrawing groups (EWGs) on the dimerization reaction seems to be further supported. Comparison of the behaviour of 3-(4-methoxyphenyl)isoxazole (**1d**) (entry 4) with that of 3-(3-methoxyphenyl)isoxazole (**1e**) (entry 5) offers a clear further confirmation of such a hypothesis.

As it is well-known, a methoxy group is a typical substituent with electronic effects that are markedly dependent on the occupied position: it behaves as an EDG when bonded to the *para* position and an EWG when instead is present in the *meta* position (see the corresponding Hammett $\sigma_{(OMe)}$ values: σ_p=−0.28; σ_m=0.10).[3]

So, while 3-(4-methoxyphenyl)isoxazole (**1d**), as previously reported,[1] affords low yields (33%) of the bis-azetidinone (**4d**), 3-(3-methoxyphenyl)-isomer (**1e**) gives high yields (79%) of **4e** (Table 2).

As expected, not very different results are instead observed in the reactions of 3-(4-fluorophenyl)- and 3-(3-fluorophenyl)isoxazole (79% and 74% yields of the corresponding bis-azetidinones **4h** and **4i**, respectively). In this case, in fact, the different position of the substituent does not cause inversion of the sign of the electronic effect (the reported $\sigma_{(F)}$ values are both positive: σ_p=0.15; σ_m=0.34).[3]

Thus, as previously observed,[1] the presence of electron-donating groups is confirmed to favour the fragmentation of iminoketene anions **2** to the detriment of their dimerization to bis-azetidinones **4**. And this, in turn, can conceivably be related to their electronic effect destabilizing the iminoketene anion and at the same time stabilizing one of the fragmentation products (ArCN **5**).

However, together with the electronic effects, we decided to also explore the steric effects of the substituent in the same reaction. This can be evaluated by comparing, for a given substituent, the behaviour of *para* versus *ortho* substituted 3-arylisoxazoles, by assuming that the electronic effects should be not much different in the two cases (comparison of σ_p with σ_δ^0 values).[4]

Examination of data referring to both electron-donating (isoxazoles **1b**,**c**) and electron-withdrawing substituents (isoxazoles **1f**,**g** and **1l**,**m**) clearly indicates, as expected, a marked dependence of the reaction on the steric effects of the substituent.

In all cases, in fact, the presence of the substituent in the *ortho* position disfavours the dimerization reaction and favours the fragmentation (see Table 2, entries 2, 3, 6, 7, 10 and 11: reference, for a given substituent, to the relative increase of the corresponding arylnitrile **5** and/or products of further reaction with LDA, on going from *para* to *ortho* substituted 3-arylisoxazoles), to an extent also roughly depending on the size of the group (calculated as Δ volume, as reported in Table 3).[5]

Similar conclusions can be drawn also by referring to different parameters for steric effects of the same groups, such as E_s values (0, −0.97, −1.24 and −2.4 for H, Cl, CH_3 and CF_3, respectively).[3]

The observed behaviour can again be related to a diminished stability of the iminoketene anion **2** compared to the fragmentation product ArCN **5**, caused, in this case, by steric effects (Scheme 3).

Table 1
Yields[a] of 3-aryl-5-hydroxy-2-isoxazolines (**6a**–**m**) from ArCNO and of 3-arylisoxazoles (**1a**–**m**) from **6a**–**m** (reference to Scheme 2)

Entry	Ar	Yield of **6a**–**m** (%)	Yield of **1a**–**m** (%)
1	Phenyl	80 (**6a**)	80 (**1a**)
2	4-Methylphenyl-	60 (**6b**)	84 (**1b**)
3	2-Methylphenyl-	74 (**6c**)	75 (**1c**)
4	4-Methoxyphenyl-	85 (**6d**)	94 (**1d**)
5	3-Methoxyphenyl-	72 (**6e**)	85 (**1e**)
6	4-Chlorophenyl-	73 (**6f**)	73 (**1f**)
7	2-Chlorophenyl-	80 (**6g**)	85 (**1g**)
8	4-Fluorophenyl-	70 (**6h**)	68 (**1h**)
9	3-Fluorophenyl-	65 (**6i**)	78 (**1i**)
10	4-(Trifluoromethyl)phenyl-	84 (**6l**)	94 (**1l**)
11	2-(Trifluoromethyl)phenyl-	72 (**6m**)	74 (**1m**)

[a] Yields refer to the products actually isolated by chromatography.

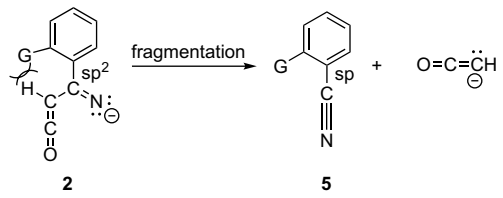
Table 2
Yields of bis-azetidinones (**4a**–**m**) and arylnitriles (**5b**, **5d**, **5e**, **5g** and **5m**) isolated by reaction of 3-arylisoxazoles (**1a**–**m**) with LDA[a]

Entry	Ar	Yield of **4a**–**m** (%)[b]	Yield of **5a**–**m** (%)[c]	Other products (%)
1	Phenyl (**1a**)	80 (**4a**)	—	—
2	4-Methylphenyl- (**1b**)	58 (**4b**)	38 (**5b**)	—
3	2-Methylphenyl- (**1c**)	7 (**4c**)	—	80 (**9**)[d]
4	4-Methoxyphenyl- (**1d**)	33 (**4d**)	56 (**5d**)	—
5	3-Methoxyphenyl- (**1e**)	79 (**4e**)	18 (**5e**)	—
6	4-Chlorophenyl- (**1f**)	70 (**4f**)	—	22[e]
7	2-Chlorophenyl- (**1g**)	40 (**4g**)	30 (**5g**)	21 (**8**)[f]
8	4-Fluorophenyl- (**1h**)	79 (**4h**)	—	—
9	3-Fluorophenyl- (**1i**)	74 (**4i**)	—	—
10	4-(Trifluoromethyl)phenyl- (**1l**)	80 (**4l**)	—	—
11	2-(Trifluoromethyl)phenyl- (**1m**)	31 (**4m**)	60 (**5m**)[g]	—

[a] Reactions were conducted in THF at 0 °C for 1 h, with isoxazole **1a**–**m**/base ratio=1:1.5.
[b] Yields refer to the products actually isolated by chromatography.
[c] Percentages determined by ^{1}H NMR spectra recorded on reaction crudes; some unreacted starting 3-arylisoxazole was also detected (**1b**, ≤4%; **1c**, ≤11%; **1d**, ≤11%).
[d] 2-Methylbenzonitrile (**5b**) in presence of LDA gives rise to dimerization to 3-(2-methylphenyl)isoquinolin-1-amine (**9**) (Scheme 5).
[e] 4-(Diisopropylamino)benzonitrile (**7**) (15%) and of 3-(diisopropylamino)benzonitrile (**8**) (7%) were also isolated (Scheme 4).
[f] 3-(Diisopropylamino)benzonitrile (**8**) was also isolated (Scheme 4).
[g] Percentages determined by ^{19}F NMR spectra recorded on reaction crudes.

Table 3
Size relative to H of groups G attached to phenyl ring, calculated as Δ molecular volume [(*Ph*–G)–(*Ph*–H)][5]

Substituent (*Ph*–G)	CPK volume (Å^3)	Δ Volume (Å^3)
Ph–H	99.1507433	—
Ph–Cl	112.323603	13.17
Ph–CH_3	117.172886	18.02
Ph–CF_3	131.654974	32.50



Scheme 3. The presence of a substituent in the *ortho* position favours the fragmentation reaction.

Transformation of the iminoketene **2** into the corresponding arylnitrile in the case of *ortho* substituted 3-arylisoxazoles is, in fact, actually accompanied by a relief of the steric hindrance, due to the smaller size and the linear geometry of the cyano group.

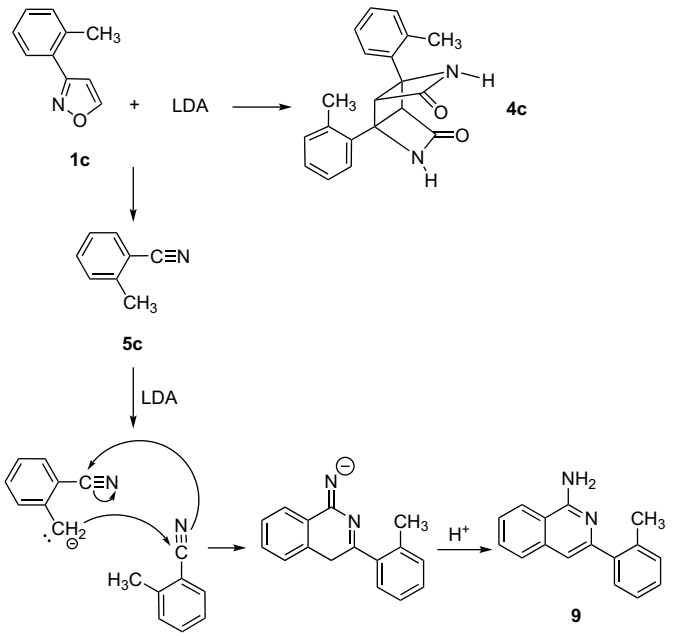
On the other hand, the present investigation also allowed us to ascertain the interesting behaviour of some formed aromatic nitriles in the presence of LDA.

The first one refers to arylnitriles derived from the fragmentation of 3-arylisoxazoles **1f** and **1g** with LDA: in both cases the formed 4-chloro- and 2-chlorobenzonitrile, respectively, further react to give (in part or completely) the products of diisopropylamino-dehalogenation (Table 2, entries 6 and 7).

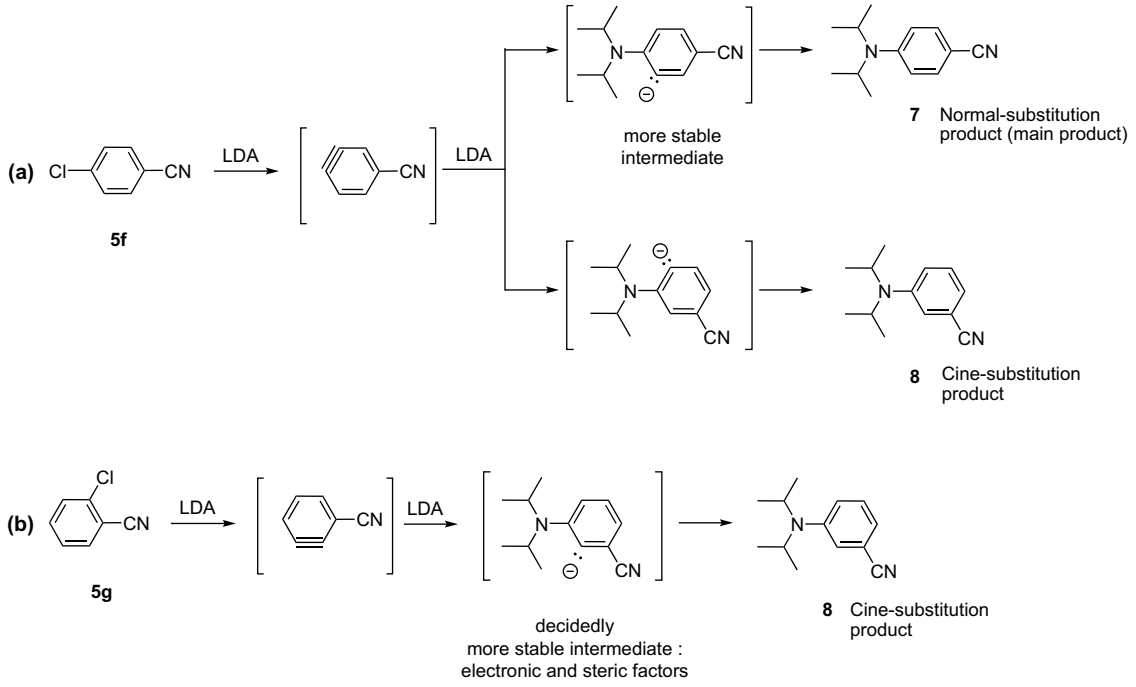
The latter reaction, however, conceivably due to the steric hindrance of the nucleophile (LDA), does not occur by S_NAr mechanism as expected by considering that the cyano group, unaffected (as it appears) by LDA under the used conditions, could in principle activate such a mechanism. So, in spite of the existing potential activation for a S_NAr reaction, a benzyne mechanism occurs instead, as revealed by isolation of both **7** and **8** (the normal- and the cine-substitution product, respectively) from 4-chlorobenzonitrile (**5f**), and of cine-substitution product **8** in the case of 2-chlorobenzonitrile (**5g**) (Table 2 and Scheme 4). Accordingly, the same results were found by reacting the commercially available chlorobenzonitriles **5f** and **5g** with LDA under the same conditions. Moreover, as expected for a benzyne mechanism, no products of diisopropylamino-dehalogenation have instead been observed starting from commercially available 4-fluorobenzonitrile (an unidentified fluorinated material was obtained in this case).

Thus, the observed behaviour may constitute an example of benzyne mechanism not induced (as commonly established)[6] by the absence of an activating group, but only (or mainly) due to a large steric hindrance of the nucleophile.

Finally, another observation concerned the reaction of 3-(2-methylphenyl)isoxazole (**1c**) with LDA. In this case, as already reported,[7] the formed 2-methylbenzonitrile (**5c**) further reacts in the presence of LDA giving rise to dimerization to 3-(2-methylphenyl)isoquinolin-1-amine (**9**) (recently tested as an antitumour agent),[8] by the mechanism outlined in Scheme 5.



Scheme 5. Reaction of 3-(2-methylphenyl)isoxazole (**1c**) with LDA.



Scheme 4. Proposed mechanism of formation of (a) 4-(diisopropylamino)benzonitrile (**7**) and 3-(diisopropylamino)benzonitrile (**8**) from 4-chlorobenzonitrile (**5f**) and (b) 3-(diisopropylamino)benzonitrile (**8**) from 2-chlorobenzonitrile (**5g**) induced by LDA.

In conclusion, the present investigation confirmed the previously observed dependence of dimerization of 3-arylisoxazoles on the electronic effects of the substituent present in the aryl moiety (reactions of *meta* and *para* substituted isoxazoles). A clear evidence of an important influence of the steric effects of the substituent on the same reaction (reactions of *ortho* substituted 3-arylisoxazoles) is also presented and a plausible explanation of both electronic and steric effects is provided.

In addition, concerning in particular the reaction of 3-(4-chlorophenyl)isoxazole (**1f**) and 3-(2-chlorophenyl) isoxazole (**1g**), an interesting behaviour with LDA of the corresponding chlorobenzonitriles generated by ring-fragmentation has also been evidenced and discussed. This reaction appears also to be an alternative synthetic approach to the *N*,*N*-diisopropylaminobenzonitrile **7** (4-DIABN)[9] and its isomer **8** (3-DIABN), widely used in dual-fluorescence and intramolecular charge transfer (ICT) studies as electron donor (D)/acceptor (A) molecules.[10,11] Further investigations are in progress on this point as well as to elucidate the chemical and biological properties of the synthesized cage-shaped bis-β-lactams.

3. Experimental section

3.1. General methods

Melting points were taken on an electrothermal apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Inova-400 MHz spectrometer, on a Bruker-Aspect 3000 console-500 MHz spectrometer and chemical shifts are reported in parts per million (δ). ^{19}F NMR spectra were recorded by using $CFCl_3$ as internal standard. Absolute values of the coupling constant are reported. FTIR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were performed by using a HP1 column (methyl siloxane; 30 m×0.32 mm×0.25 μm film thickness) on a HP 6890 model, Series II. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator; the spots on the TLC were observed under ultraviolet light or were visualized by I_2 vapour. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC–MS analyses were performed on an HP 5995C model and elemental analyses on an Elemental Analyzer 1106-Carlo Erba-instrument. MS-ESI analyses were performed on Agilent 1100 LC/MSD trap system VL.

3.2. Materials

Tetrahydrofuran (THF) from commercial source was purified by distillation (twice) from sodium wire under nitrogen atmosphere. DMF from commercial source was purified by distillation from CaH_2 under reduced pressure. Standardized (2.5 M) *n*-butyllithium in hexanes was purchased from Aldrich Chemical Co. and its titration was performed with *N*-pivaloyl-*o*-toluidine.[12] Diisopropylamine from Aldrich Chemical Co. was purified by distillation from CaH_2. All other chemicals and solvents were commercial grade further purified by distillation or crystallization prior to use.

All the used 3-arylisoxazoles **1a**–**m** were prepared via the corresponding 3-aryl-5-hydroxy-2-isoxazolines **6a**–**m**, by using the previously described procedure.[1,2] Arylnitrile oxides were prepared from aldehydes through their conversion into the corresponding oximes and then into benzohydroximinoyl chlorides.[2,13] These were finally converted into nitrile oxides by treatment with NEt_3, followed by *vacuum* filtration of the formed $NEt_3 \cdot HCl$ from the reaction mixture.

Oximes, prepared from reaction of aldehydes/EtOH and $NH_2OH \cdot HCl$/aq NaOH,[1,2] had analytical and spectroscopic data identical to those previously reported or commercially available compounds.

3.2.1. 2-Methylbenzaldehyde oxime[14,15]

FTIR (neat): 3210, 3071, 2992, 2922, 2870, 2744, 1625, 1498, 1454, 1425, 1318, 1291, 1227, 1188, 978, 954, 874, 792, 751, 711 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.50–9.0 (br s, 1H, OH: exchanges with D_2O), 8.50 (s, 1H), 7.72–7.74 (m, 1H, aromatic proton), 7.32–7.35 (m, 1H, aromatic proton), 7.25–7.29 (m, 2H, aromatic protons), 2.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 149.2, 136.8, 130.8, 130.1, 129.8, 126.6, 126.2, 19.6. GC–MS (70 eV) *m*/*z* (rel int.): 135 (M^+, 69), 120 (59), 119 (11), 118 (92), 117 (100), 116 (22), 91 (56), 90 (38), 89 (39), 77 (13), 65 (25), 63 (21), 51 (11).

3.2.2. 3-Methoxybenzaldehyde oxime[16]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.0–8.40 (br s, 1H, OH: exchanges with D_2O), 8.14 (s, 1H), 7.32–7.28 (m, 1H, aromatic proton), 7.17–7.12 (m, 2H, aromatic protons), 6.97–6.93 (m, 1H, aromatic proton), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.8, 150.3, 133.2, 129.8, 120.1, 116.4, 111.2, 55.3.

3.2.3. 4-Chlorobenzaldehyde oxime[14,17]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.10 (s, 1H), 7.82–7.60 (m, 1H, OH: exchanges with D_2O), 7.53–7.50 (d, 2H, J=8.4 Hz, aromatic protons), 7.37–7.34 (d, 2H, J=8.4 Hz, aromatic protons). GC–MS (70 eV) *m*/*z* (rel int.): 155 (M^+, 100), 134 (22), 108 (58), 92(21), 77 (29), 63 (17), 51 (9).

3.2.4. 3-Fluorobenzaldehyde oxime[18]

Yield 92%. Light semi-solid. FTIR (neat): 3307, 3017, 2934, 2854, 1584, 1489, 1448, 1326, 1271, 1257, 1140, 953, 946, 862, 779, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.00–9.40 (br s, 1H, OH: exchanges with D_2O), 8.18 (s, 1H), 7.38–7.33 (m, 3H, aromatic protons), 7.12–7.06 (m, 1H, aromatic proton). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 162.8 (d, $^1J_{19F-13C}$=246 Hz), 149.5 (d, $^4J_{19F-13C}$=2.7 Hz), 133.8 (d, $^3J_{19F-13C}$=8.0 Hz), 130.3 (d, $^3J_{19F-13C}$=8.0 Hz), 123.1 (d, $^4J_{19F-13C}$=3.0 Hz), 117.0 (d, $^2J_{19F-13C}$=21.8 Hz), 113.3 (d, $^2J_{19F-13C}$=22.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −116.4 (m).

3.2.5. 2-(Trifluoromethyl)benzaldehyde oxime[14,19]

Yield 95%. FTIR (neat): 3306, 3080, 3026, 2927, 1580, 1495, 1450, 1317, 1280, 1180, 1157, 1111, 1036, 975, 875, 763, 670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.40–9.30 (br s, 1H, OH: exchanges with D_2O), 8.61 (m, 1H), 7.99–7.97 (m, 1H, aromatic proton), 7.70–7.67 (m, 1H, aromatic proton), 7.56–7.52 (m, 1H, aromatic proton), 7.49–7.45 (m, 1H, aromatic proton). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 147.4 (m), 132.0, 129.9 (m), 129.7, 128.4 (q, $^2J_{19F-13C}$=30.9 Hz), 127.3, 125.9 (q, $^3J_{19F-13C}$=5.5 Hz), 123.9 (q, $^1J_{19F-13C}$=273.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.8.

3.3. Synthesis of benzohydroximinoyl chlorides: general procedure[2,13]

In a round-bottom flask equipped with magnetic stirrer the benzaldoxime (3.483 g, 0.0251 mol) was dissolved in anhydrous DMF (60 mL), then the solution was cooled to 0 °C. NCS (3.686 g, 0.0276 mol) was slowly added and the suspension was stirred to 0 °C. When the reaction was completed, water was added to the reaction mixture became a limpid yellow solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with water to remove succinimide and then the solution was dried over anhydrous Na_2SO_4. Benzohydroximinoyl chlorides (obtained in 77–90% yield after evaporation of the solvent under vacuum) had analytical and spectroscopic data identical to those previously reported or commercially available compounds.

3.3.1. N-Hydroxy-2-methylbenzimidoyl chloride[14,15]

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.30–8.50 (s, 1H, br s, OH: exchanges with D_2O), 7.21–7.47 (m, 4H, aromatic protons), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.9, 137.0, 133.0, 130.8, 130.1, 129.5, 125.9, 20.2.

3.3.2. 3-Fluoro-N-hydroxybenzimidoyl chloride[20]

Yield 86%. Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.70–9.50 (br s, 1H, OH: exchanges with D_2O), 7.60–7.58 (m, 1H, aromatic proton), 7.52–7.49 (m, 1H, aromatic proton), 7.37–7.30 (m, 1H, aromatic proton), 7.13–7.08 (m, 1H, aromatic proton). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 162.4 (d, $^1J_{19F-13C}$=247 Hz), 138.3 (d, $^4J_{19F-13C}$=3.3 Hz), 134.3 (d, $^3J_{19F-13C}$=8.6 Hz), 129.9 (d, $^3J_{19F-13C}$=8.1 Hz), 122.7 (d, $^4J_{19F-13C}$=3.3 Hz), 117.5 (d, $^2J_{19F-13C}$=21.5 Hz), 114.0 (d, $^2J_{19F-13C}$=24.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.8.

3.3.3. N-Hydroxy-2-trifluoromethylbenzimidoyl chloride[14,21]

Yield 83%. White semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.60–10.40 (br s, 1H, OH: exchanges with D_2O), 7.65–7.62 (m, 1H, aromatic proton), 7.54–7.45 (m, 3H, aromatic protons). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.9. ^{13}C NMR (125 MHz, $CDCl_3$, δ): 164.1, 135.0, 131.9 (q, $^4J_{19F-13C}$=1.9 Hz), 131.8, 130.9, 130.1, 128.4 (q, $^2J_{19F-13C}$=31.5 Hz), 126.3 (q, $^3J_{19F-13C}$=4.8 Hz), 123.3 (q, $^1J_{19F-13C}$=273.7 Hz).

3.4. Synthesis of 3-aryl-5-hydroxy-2-isoxazolines (6a–m): general procedure[1,2]

A solution of the enolate ion of acetaldehyde in anhydrous THF (10 mL) was dropwise added at room temperature to a solution of arylnitrile oxide in THF (10 mL) contained in a nitrogen-flushed three-necked flask equipped with a magnetic stirrer. After the reaction was completed, the reaction mixture was quenched by adding aq NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=70:30) of the residue afforded the 3-aryl-5-hydroxy-2-isoxazolines **6a–m** in 60–85% yields (Table 1). 5-Hydroxy-3-aryl-2-isoxazoline (**6a**,[2] **6b**, **6d**, **6g**,[2] **6h**, **6l**)[1] had analytical and spectroscopic data identical to those previously reported.

*3.4.1. 3-(2-Methylphenyl)-5-hydroxy-2-isoxazoline (**6c**)*

Yield 74%, 1.415 g. Light yellow oil. FTIR (KBr): 3383, 3063, 2960, 2925, 1603, 1493, 1455, 1342, 1176, 1076, 921, 839, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35–7.20 (m, 4H, aromatic protons), 6.00 (d, 1H, J=6.7 Hz), 4.6–4.5 (br s, 1H, OH: exchanges with D_2O), 3.46 (dd, 1H, J=6.7 and 17.5 Hz), 3.25 (d, 1H, J=17.5 Hz), 2.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8, 137.9, 131.4, 129.5, 129.1, 128.0, 125.7, 96.9, 44.9, 22.6. GC–MS (70 eV) m/z (rel int.): 177 (M^+, 63), 162 (22), 160 (56), 134 (17), 133 (13), 132 (38), 131 (29), 130 (100), 117 (27), 116 (20), 115 (33), 104 (17), 103 (15), 91 (31), 89 (18), 78 (16), 77 (21), 65 (18), 63 (12). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.80; H, 6.24; N, 7.52.

*3.4.2. 3-(3-Methoxyphenyl)-5-hydroxy-2-isoxazoline (**6e**)*

Yield 72%, 3.640 g. Light yellow oil. FTIR (neat): 3391, 3080, 2938, 2840, 1607, 1574, 1460, 1433, 1348, 1287, 1260, 1218, 1177, 1080, 1033, 881, 789, 689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.32–7.27 (m, 2H, aromatic protons), 7.20–7.17 (m, 1H aromatic proton), 6.98–6.95 (m, 1H aromatic proton), 6.04 (dd, 1H, J=6.6 and 1.5 Hz), 4.0–3.6 (br s, 1H, OH: exchanges with D_2O), 3.82 (s, 3H), 3.41 (dd, 1H, J=6.6 and 17.6 Hz), 3.23 (dd, 1H, J=17.6 and 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.6, 156.8, 130.2, 129.7, 119.6, 116.8, 114.1, 98.0, 55.3, 42.5. GC–MS (70 eV) m/z (rel int.): 193 (M^+, 63), 176 (18), 175 (100), 174 (77), 165 (12), 150 (13), 149 (14), 147 (27), 146 (10), 134 (11), 133 (19), 132 (22), 107 (17), 104 (13), 103 (10), 92 (29), 91 (13), 77 (44), 76 (13), 64 (16), 63 (17). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.30; H, 5.88; N, 7.33.

*3.4.3. 3-(4-Chlorophenyl)-5-hydroxy-2-isoxazoline (**6f**)*[22]

Yield 73%, 2.042 g. Mp 128.0–129.0 °C. Light yellow crystals. FTIR (KBr): 3344, 2921, 2404, 1852, 1917, 1741, 1595, 1491, 1462, 1404, 1351, 1274, 1242, 1175, 1085, 1012, 892, 874, 823 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.63–7.58 (m, 2H, aromatic protons), 7.39–7.35 (m, 2H, aromatic protons), 6.06 (dd, 1H, J=6.5 and 1.65 Hz), 4.00–3.80 (br s, 1H, OH: exchange with D_2O), 3.40 (dd, 1H, J=6.5 and 17.5 Hz), 3.21 (dd, 1H, J=17.5 and 1.65 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 156.2, 136.7, 129.3, 128.4, 127.7, 98.4, 42.6. GC–MS (70 eV) m/z (rel int.): 197 (M^+, 69), 180 (19), 178 (42), 170 (26), 168 (97), 153 (35), 139 (34), 137 (100), 125 (22), 111 (45), 102 (44), 75 (43), 63 (15), 51 (25).

*3.4.4. 3-(3-Fluorophenyl)-5-hydroxy-2-isoxazoline (**6i**)*

Yield 65%, 2.679 g. Mp 167–168 °C. Light yellow crystals. FTIR (KBr): 3221, 3065, 2964, 2848, 1599, 1574, 1494, 1429, 1366, 1274, 1249, 1186, 1089, 918, 873, 790 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2CO$, δ): 7.58–7.46 (m, 3H, aromatic protons), 7.25–7.19 (m, 1H, aromatic proton), 6.2–6.05 (br s, 1H, OH: exchanges with D_2O), 6.03 (dd, 1H, J=6.9 and 1.6 Hz), 3.52 (dd, 1H, J=6.9 and 17.8 Hz), 3.20 (dd, 1H, J=17.8 and 1.6 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2CO$, δ): 164.6 (d, $^1J_{19F-13C}$=244 Hz), 157.0 (d, $^4J_{19F-13C}$=3.0 Hz), 134.3 (d, $^3J_{19F-13C}$=8.0 Hz), 132.6 (d, $^3J_{19F-13C}$=8.4 Hz), 124.5 (d, $^4J_{19F-13C}$=3.0 Hz), 118.4 (d, $^2J_{19F-13C}$=21.4 Hz), 114.9 (d, $^2J_{19F-13C}$=23.3 Hz), 100.4, 43.4. ^{19}F NMR (376 MHz, $(CD_3)_2CO$, δ): −109.2. GC–MS (70 eV) m/z (rel int.): 181 (M^+, 55), 164 (20), 163 (76), 162 (78), 153 (41), 152 (47), 135 (29), 134 (28), 122 (20), 121 (58), 109 (21), 108 (19), 107 (32), 101 (21), 96 (19), 95 (100), 81 (11), 75 (46), 57 (15), 50 (10). Anal. Calcd for $C_9H_8FNO_2$: C, 59.67; H, 4.45; N, 7.73. Found: C, 60.05; H, 4.53; N, 7.73.

*3.4.5. 3-(2-(Trifluoromethyl)phenyl)-5-hydroxy-2-isoxazoline (**6m**)*

Yield 82%, 3.247 g. Light yellow oil. FTIR (neat): 3382, 3077, 2962, 2927, 2851, 1606, 1451, 1316, 1271, 1175, 1116, 1079, 1036, 840, 770 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.76–7.73 (m, 1H, aromatic proton), 7.60–7.53 (m, 3H, aromatic protons), 6.05 (dd, 1H, J=6.6 and 1.5 Hz), 4.4–3.9 (br s, 1H, OH: exchanges with D_2O), 3.49 (dd, 1H, J=6.6 and 17.9 Hz), 3.16 (dd, 1H, J=17.9 and 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 156.4, 132.0 (m), 129.9, 128.5 (q, $^2J_{19F-13C}$=31.5 Hz), 128.3 (q, $^4J_{19F-13C}$=1.9 Hz), 126.6 (q, $^3J_{19F-13C}$=5.7 Hz), 123.7 (q, $^1J_{19F-13C}$=273.4 Hz), 98.3, 46.0 (m). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.9. GC–MS (70 eV) m/z (rel int.): 231 (M^+, 100), 214 (16), 213 (97), 212 (95), 188 (35), 185 (65), 184 (51), 183 (52), 171 (38), 168 (45), 166 (47), 165 (50), 164 (20), 163 (21), 162 (78), 152 (49), 151 (97), 145 (97), 133 (38), 121 (30), 95 (34), 75 (38). Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 51.70; H, 3.53; N, 6.30.

3.5. Synthesis of 3-arylisoxazoles (1a–m): general procedure[1,2]

In a round-bottom flask equipped with magnetic stirrer, MeONa (0.654 g, 12.7 mmol) was added to a solution of 3-aryl-5-hydroxy-2-isoxazolines **6a–m** (1.885 g, 11.5 mmol) in MeOH (30 mL). The reaction mixture was then heated under reflux. After the reaction was completed, the reaction mixture was quenched by adding aq NH_4Cl. MeOH was evaporated under reduced pressure and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=10:1) of the residue affords 3-arylisoxazoles **1a–m** in 65–94% yields (Table 1). 3-

Phenylisoxazole (**1a**),[2] 3-(4-methylphenyl)isoxazole (**1b**),[1,23] 3-(4-methoxyphenyl) isoxazole (**1d**)[1,24] and 3-(4-fluorophenyl)isoxazole (**1h**),[1,25] 3-(4-trifluoromethyphenyl)isoxazole (**1l**)[1,26] had analytical and spectroscopic data identical to those previously reported.

*3.5.1. 3-(2-Methylphenyl)isoxazole (**1c**)*

Yield 75%, 0.820 g. Colourless oil. FTIR (neat): 3153, 3120, 2956, 2925, 1606, 1553, 1460, 1386, 1120, 1086, 874, 762, 726. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.39 (d, 1H, J=1.5 Hz), 7.45–7.43 (m, 1H, aromatic proton), 7.28–7.20 (m, 3H, aromatic protons), 6.46 (d, 1H, J=1.5 Hz), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 161.9, 157.9, 136.8, 131.0, 129.43, 129.40, 128.4, 125.9, 105.0, 21.0. GC–MS (70 eV) m/z (rel int.): 159 (M^+, 63), 158 (63), 130 (100), 103 (20), 91 (16), 89 (14), 77 (15), 65 (20), 51 (11). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.40; H, 5.68; N, 8.50.

*3.5.2. 3-(3-Methoxyphenyl)isoxazole (**1e**)*

Yield 74%, 2.431 g. Light yellow oil. FTIR (neat): 3147, 3125, 3004, 2939, 2838, 1588, 1556, 1472, 1436, 1385, 1320, 1295, 1236, 1123, 1039, 885, 830, 777, 771, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.46 (d, 1H, J=1.8 Hz), 7.41–7.40 (m, 1H, aromatic proton), 7.38–7.36 (d, 2H, aromatic protons), 7.01–6.98 (m, 1H, aromatic proton), 6.66 (d, 1H, J=1.8 Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.4, 159.9, 158.9, 129.98, 129.96, 119.4, 116.1, 111.8, 102.6, 55.4. GC–MS (70 eV) m/z (rel int.): 175 (M^+, 100), 174 (75), 132 (16), 107 (12), 92 (22), 77 (32), 76 (10), 64 (12), 63 (13). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.41; H, 5.01; N, 7.86.

*3.5.3. 3-(4-Chlorophenyl)isoxazole (**1f**)[22]*

Yield 73%, 0.160 g. Mp 70.0–71.0 °C. Light yellow crystals. FTIR (KBr): 3151, 3129, 3078, 2925, 2853, 1664, 1548, 1548, 1503, 1430, 1372, 1274, 1121, 1099, 1046, 1014, 946, 887, 832, 782, 719, 683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.47 (d, 1H, J=1.8 Hz), 7.76 (d, 2H, J=8.4 Hz, aromatic protons), 7.44 (d, 2H, J=8.4 Hz, aromatic protons), 6.64 (d, 1H, J=1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 160.5, 159.1, 136.0, 129.2, 128.1, 127.2, 102.3. GC–MS (70 eV) m/z (rel int.): 179 (M^+, 140), 153 (11), 152 (15), 151 (30), 150 (32), 123 (15), 113 (15), 111 (36), 89 (22), 75 (34), 74 (11), 50 (12).

*3.5.4. 3-(3-Fluorophenyl)isoxazole (**1i**)*

Yield 78%, 1.790 g. Light oil. FTIR (neat): 3153, 3129, 3073, 2960, 2932, 2873, 1616, 1588, 1557, 1505, 1464, 1422, 1384, 1296, 1269, 1207, 1122, 1097, 973, 881, 845, 775, 710, 681 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.48 (d, 1H, J=1.4 Hz), 7.61–7.59 (m, 1H, aromatic proton), 7.56–7.53 (m, 1H, aromatic proton), 7.46–7.41 (m, 1H, aromatic proton), 7.17–7.12 (m, 1H, aromatic proton), 6.65 (d, 1H, J=1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 163.0 (d, $^1J_{19F-13C}$=247 Hz), 160.6 (d, $^4J_{19F-13C}$=2.9 Hz), 159.2, 130.8 (d, $^3J_{19F-13C}$=7.6 Hz), 130.6 (d, $^3J_{19F-13C}$=8.6 Hz), 122.6 (d, $^4J_{19F-13C}$=2.9 Hz), 116.9 (d, $^2J_{19F-13C}$=21.0 Hz), 113.9 (d, $^2J_{19F-13C}$=22.9 Hz), 102.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −116.8. GC–MS (70 eV) m/z (rel int.): 163 (M^+, 98), 162 (100), 135 (11), 134 (23), 108 (16), 107 (23), 95 (41), 75 (21). Anal. Calcd for C_9H_6FNO: C, 66.26; H, 3.71; N, 8.59. Found: C, 65.90; H, 3.69; N, 8.50.

*3.5.5. 3-[2-(Trifluoromethyl)phenyl]isoxazole (**1m**)*

Yield 82%, 2.117 g. Light yellow oil. FTIR (neat): 3160, 3130, 3076, 2929, 2856, 1609, 1584, 1555, 1504, 1427, 1392, 1316, 1266, 1176, 1125, 1060, 1035, 888, 770, 690 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.48 (d, 1H, J=1.6 Hz), 7.81–7.79 (m, 1H, aromatic proton), 7.65–7.56 (m, 3H, aromatic protons), 6.58–6.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 160.5, 158.3, 129.7, 128.9 (q, $^2J_{19F-13C}$=30.9 Hz), 128.1 (m), 126.4 (q, $^3J_{19F-13C}$=5.2 Hz), 123.7 (q, $^1J_{19F-13C}$=273.5 Hz), 105.9 (q, $^5J_{19F-13C}$=3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.4. GC–MS (70 eV) m/z (rel int.): 213 (M^+, 100), 212 (97), 184 (31), 165 (29), 164 (18), 145 (35), 138 (7), 134 (10), 125 (10), 107 (6), 95 (10), 75 (10). Anal. Calcd for $C_{10}H_6F_3NO$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.30; H, 2.88; N, 6.50.

3.6. Reaction of 3-arylisoxazoles (1a–m) with lithium diisopropylamide: general procedure

A 2.5 M solution of *n*-BuLi in hexanes (0.310 mL, 0.776 mmol) was added to a solution of the diisopropylamine (0.853 mmol) in THF (2 mL) at 0 °C under nitrogen atmosphere, using a nitrogen-flushed three-necked flask equipped with a magnetic stirrer and a nitrogen inlet. After 10 min, the solution of the 3-arylisoxazoles **1a–m** (75 mg, 0.517 mmol) in THF (1 mL) was dropwise added and the obtained brown reaction mixture, kept at 0 °C, was stirred for 1 h and then quenched by adding aq NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=6:4) of the residue afforded the *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones **4a–m** as indicated in the Scheme 3, Tables 1 and 2. ^{1}H NMR signal (δ=4.10÷4.35 ppm) attributed to the proton at C_5 was a doublet with long-range coupling constant ^4J=2.0÷3.2 Hz. ^4J (≠0 Hz) was due to the 'W conformation' of the four σ bonds between H_5 and H_{amidic}. H_{amidic} peak was not split by H_5, its signal was broadened by the quadrupolar interaction.

Analytical and spectroscopic data of *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones **4a**, **4b**, **4d**, **4h** and **4l** were previously reported.[1] Arylnitriles **5b**, **5d**, **5e**, **5g** and **5m**, isolated as product of the reaction mentioned above (Scheme 1 and Table 2) had the same analytical and spectroscopic data of the commercially available compounds.

*3.6.1. syn 2,6-Bis(2-methylphenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**4c**)*

Yield 7%, 0.0036 g. Yellow semi-solid. FTIR (neat): 3200, 2922, 2847, 1742, 1453, 1350, 1257, 1237, 1093, 1030, 757, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.85–8.75 (br s, 2H, NH protons: exchange with D_2O), 7.30–7.26 (m, 4H, aromatic protons), 7.19–7.15 (m, 2H, aromatic protons), 7.11–7.08 (m, 2H, aromatic protons), 4.22 (d, 2H, J=3.2 Hz), 2.47 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.3, 136.3, 131.5, 130.9, 128.8, 126.2, 125.7, 61.6, 53.9, 19.5. LC–MS (ESI$^+$): 341 $[M+Na]^+$.

*3.6.2. syn 2,6-Bis(3-methoxyphenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**4e**)*

Yield 79%, 0.039 g. Mp 135.0–136 °C. Light orange powder. FTIR (KBr): 3432, 3242, 2924, 2853, 1750, 1609, 1581, 1450, 1384, 1321, 1290, 1260, 1215, 1038, 789, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.99–7.97 (br s, 2H, NH protons: exchange with D_2O), 7.36–7.32 (m, 2H, aromatic protons), 7.00–6.94 (m, 4H, aromatic protons), 6.91–6.88 (m, 2H, aromatic protons), 4.23 (d, 2H, J=2.2 Hz), 3.83 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.8, 160.0, 138.3, 130.1, 118.1, 113.7, 111.8, 64.0, 55.4, 52.0. LC–MS (ESI$^+$): 373 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.66; H, 5.27; N, 7.80.

*3.6.3. syn 2,6-Bis(4-chlorophenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**4f**)*

Yield 70%, 0.035 g. Pink powder. Mp 129.6–130.0 °C (dec). FTIR (KBr): 3425, 3278, 2924, 2856, 1760, 1734, 1091, 816, 745, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.10–7.90 (br s, 2H, NH protons: exchange with D_2O), 7.43–7.41 (m, 4H, aromatic protons), 7.35–7.33 (m, 4H, aromatic protons), 4.21 (d, 2H, J=2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.0, 135.3, 135.0, 129.5, 129.1, 127.5, 64.2, 51.9. LC–MS (ESI$^-$): 357 $[M-H]^-$. Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.27; H, 3.42; N, 7.90.

*3.6.4. syn 2,6-Bis(2-chlorophenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**4g**)*

Yield 40%, 0.020 g. Light powder. Mp 207–208 °C (dec). FTIR (KBr): 3228, 2924, 2853, 1768, 1750, 1060, 759 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.30–8.10 (br s, 2H, NH protons: exchange with D_2O), 7.46–7.43 (m, 2H, aromatic protons), 7.35–7.28 (m, 6H, aromatic protons), 4.45 (d, 2H, J=2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.2, 134.5, 133.2, 130.4, 130.2, 128.1, 127.1, 61.3, 53.3. LC–MS (ESI$^+$): 381 [M+Na]$^+$. Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.20; H, 3.22; N, 7.80.

*3.6.5. syn 2,6-Bis(3-fluorophenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**4i**)*

Yield 74%, 0.037 g. Light crystals. Mp 158–160 °C (dec). FTIR (KBr): 3435, 3246, 3087, 2957, 2924, 2854, 1738, 1613, 1587, 1487, 1440, 1383, 1261, 1105, 794 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.54–8.53 (br s, 2H, NH protons: exchange with D_2O), 7.45–7.39 (m, 2H, aromatic protons), 7.22–7.19 (m, 2H, aromatic protons), 7.16–7.05 (m, 4H, aromatic protons), 4.22 (d, 2H, J=2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.8, 163.0 (d, $^1J_{19F-13C}$=248 Hz), 139.2 (d, $^3J_{19F-13C}$=7.2 Hz), 130.8 (d, $^3J_{19F-13C}$=8.4 Hz), 121.5 (d, $^4J_{19F-13C}$=3.0 Hz), 115.6 (d, $^2J_{19F-13C}$=21.0 Hz), 113.2 (d, $^2J_{19F-13C}$=22.9 Hz), 64.0, 51.8 (d, $^4J_{19F-13C}$=2.3 Hz). LC–MS (ESI$^+$): 349 [M+Na]$^+$. Anal. Calcd for $C_{18}H_{12}F_2N_2O_2$: C, 66.26; H, 3.71; N, 8.59. Found: C, 66.36; H, 3.82; N, 8.66.

*3.6.6. syn 2,6-Bis-3-(2-(trifluoromethyl)phenyl)-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (**4m**)*

Yield 30%, 0.015 g (white solid). Mp 240.1–241.8 °C (dec). FTIR (KBr): 3240, 2923, 2853, 1759, 1607, 1450, 1315, 1263, 1170, 1123, 1109, 1033, 766 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2CO_3$, δ): 8.30–8.16 (br s, 2H, NH protons: exchange with D_2O), 7.90–7.85 (m, 2H, aromatic protons), 7.71–7.63 (m, 6H, aromatic protons), 4.65 (d, 2H, J=2.1 Hz). ^{13}C NMR (125 MHz, $(CD_3)_2CO_3$, δ): 164.0, 135.9 (m), 133.2, 129.5, 129.2, 128.0 (q, $^2J_{19F-13C}$=31.5 Hz), 127.9 (m), 124.7 (q, $^1J_{19F-13C}$=273.2 Hz), 63.3, 52.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −53.9. LC–MS (ESI$^+$): 449 [M+Na]$^+$(100). Anal. Calcd for $C_{20}H_{12}F_6N_2O_2$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.31; H, 2.93; N, 6.43.

*3.6.7. 4-(Diisopropylamino)benzonitrile (**7**)*[9]

Yield 15%, 0.017 g. White crystals. Mp 85–86 °C (lit. 81–84 °C).[9] FTIR (neat): 2969, 2925, 2851, 2212, 1602, 1517, 1334, 1302, 1182, 1156, 1120, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.41–7.39 (m, 2H, aromatic protons), 6.78–6.75 (m, 2H, aromatic protons), 3.92 (septuplet, 2H, J=6.8 Hz), 1.30 (d, 12H, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.9, 132.9, 120.7, 114.5, 96.9, 47.4, 20.7. GC–MS (70 eV) m/z (rel int.): 202 (M$^+$, 17), 187 (56), 145 (100), 129 (8), 102 (15), 43 (8), 41 (7).

*3.6.8. 3-(Diisopropylamino)benzonitrile (**8**)*

Yield 7–22%, 0.008–0.025 g. Yellow semi-solid. FTIR (neat): 2971, 2930, 2873, 2853, 2227, 1591, 1496, 1369, 1300, 1195, 1180, 999, 775, 689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.23–7.19 (m, 1H, aromatic proton), 7.03–7.00 (m, 2H, aromatic protons), 6.95–6.92 (m, 1H, aromatic proton), 3.82 (septuplet, 2H, J=6.8 Hz), 1.30 (d, 12H, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.3, 129.2, 120.9, 119.9, 119.3, 112.4, 47.5, 21.0. GC–MS (70 eV) m/z (rel int.): 202 (M$^+$, 11), 187 (47), 159 (5), 146 (10), 145 (100), 129 (6), 117 (3), 102 (12), 43(7), 41(7). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.03; H, 8.83; N, 13.74.

*3.6.9. 3-(2-Methylphenyl)isoquinolin-1-amine (**9**)*[7]

Yield 80%, 0.029 g. FTIR (neat): 3329, 3199, 3056, 2954, 2924, 2853, 1650, 1632, 1588, 1564, 1498, 1432, 1370, 1337, 764, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.91–7.89 (m, 1H, aromatic proton), 7.75–7.72 (m, 1H, aromatic proton), 7.68–7.64 (m, 1H, aromatic proton), 7.54–7.50 (m, 1H, aromatic proton), 7.45–7.43 (m, 1H, aromatic proton), 7.30–7.26 (m, 3H, aromatic protons), 7.09 (s, 1H aromatic proton), 5.90–5.70 (br s, 2H, NH: exchange with D_2O), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 155.4, 150.9, 137.7, 136.0, 130.7, 130.6, 129.6, 128.0, 127.3, 126.2, 125.7, 122.8, 116.4, 112.0, 20.3. GC–MS (70 eV) m/z (rel int.): 234 (M$^+$, 50), 233 (100), 216 (17), 189 (5), 116 (14).

Acknowledgements

This work was financially supported by National Project 'Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni' MiUR (Rome), and the University of Bari. Thanks are due to Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR, Bari) for NMR facilities.

Supplementary data

NMR spectra for the new synthesized compounds are available free of charge in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.063.

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