Simple Synthesis of 2-Aminoaryliminophosphoranes from *N*-Aryl-2-nitrosoanilines and Their Application in 2-Aminobenzimidazole Synthesis

Emilia Łukasik, Zbigniew Wróbel*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland
Fax +48(22)6326681; E-mail: zbigniew.wrobel@icho.edu.pl

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Abstract: Condensation of *N*-aryl-2-nitrosoanilines with triphenylphosphine leads efficiently to substituted aryliminophosphoranes which, in turn, react with alkyl isocyanates furnishing 2-alkylaminobenzimidazole derivatives in high yields.

Key words: cyclization, condensation, heterocycles, annulation

Aryliminophosphoranes were first reported 1919.[1a] Since then several methods for their synthesis have been developed including the Staudinger reaction of aromatic azides with phosphines,[1,2] coupling of amines and phosphines with the help of halogenating agents,[3] oxidants such as alkyl azodicarboxylates[4] or acetylenedicarboxylates.[5] In very few cases, they have been obtained from nitro compounds[6] or via elaborate rearrangements.[5] Preparation of aryliminophosphoranes from nitrosoarenes is, to our knowledge, so far unknown.[7]

In 2007 we described a simple and efficient method for the synthesis of *N*-aryl-2-nitrosoanilines from nitroarenes and anilines in basic media.[8] We proved the versatility of these compounds especially for the synthesis of some nitrogen-containing heterocyclic frameworks.[8a,9]

Having numerous 2-nitrosoanilines **1** readily accessible, we tried to access aryliminophosphoranes by the reaction of **1** with triphenylphosphine (**2**). The procedure was very simple and comprised portionwise addition of the solid substrate to a suspension of an excess of triphenylphosphine in dry acetonitrile, without exclusion of air or moisture, followed by stirring at room temperature until completion of reaction. The reaction proceeded smoothly furnishing products **3** in almost quantitative yields (Table 1).[10] In most cases the products precipitated from the reaction mixture in a pure form. Additional column chromatography of the filtrate improved the isolated yield marginally. Since nitroso compounds **1** are more accessible than the corresponding azides, this approach appears to be a valuable alternative to the Staudinger method.

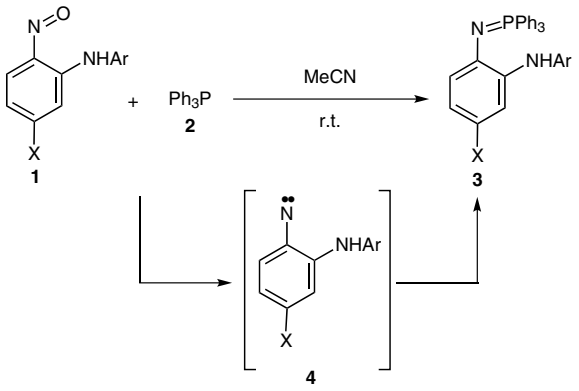
The mechanism of the reaction probably involves the Cadogan formation of nitrene **4**,[7a] an active intermediate, which condenses with an excess of **2** to form the final 4-X-2-*N*-aryl-1-*N*-(triphenyl-λ^5-phosphanylidene)benzene-1,2-diamine **3** (Scheme 1).

The reaction appears to be general with regard to substituents *para* to the nitroso group as well as the aryl group in the *N*-aryl-2-nitrosoanilines. Steric hindrance caused by two *ortho*-methyl groups in the *N*-aryl ring (Table 1, entry 3) lowered the yield of the product only slightly. 2-Arylamino triphenyliminophosphoranes **3** turned out to be stable, crystalline compounds which can be shelf-stored and purified by chromatography without notable decomposition.[11] When stirred in wet THF, **3g** remained unchanged, but after acidification slow hydrolysis/reduction to the corresponding diamine was observed. The process was much faster in refluxing ethanolic HCl;[12] as a result **3g** was converted into 5-chloro-1-*N*-(4-chlorophenyl)benzene-1,2-diamine, albeit in rather low yield.

Table 1 Synthesis of Aryliminophosphoranes **3**

Entry	X	Ar	Product **3**	Yield (%)[a]
1	Cl	4-MeC_6H_4	**3a**	98
2	OMe	4-MeC_6H_4	**3b**	96
3	Cl	2,6-Me$_2C_6H_3$	**3c**	85
4	F	4-ClC_6H_4	**3d**	93
5	Br	4-MeC_6H_4	**3e**	94
6	Cl	2-MeC_6H_4	**3f**	89
7	Cl	4-ClC_6H_4	**3g**	90
8	Ph	4-MeC_6H_4	**3h**	97

[a] Isolated yield.



Scheme 1

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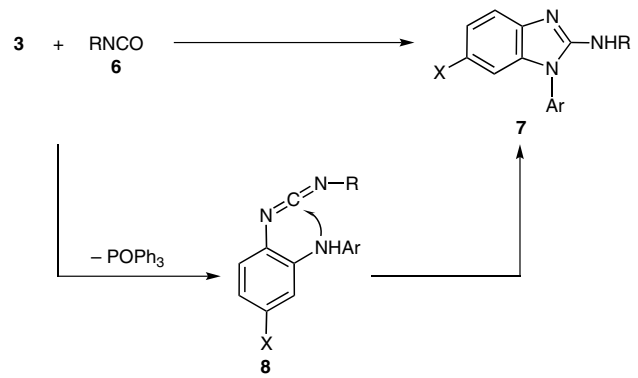
4-X-2-*N*-Aryl-1-*N*-(triphenyl-λ^5-phosphanylidene)benzene-1,2-diamines were then applied to the synthesis of 1-aryl-2-aminobenzimidazoles. For this purpose we adopted the known reaction of iminophosphoranes with isocyanates, initially leading to carbodiimides, susceptible to further conversions.[13] In our case intramolecular addition of the nucleophilic *ortho*-amine function to the carbodiimide would be expected to lead to the 2-aminobenzimidazole framework (Scheme 2).[14] In fact, the reaction of **3** with alkyl isocyanates proceeded smoothly in dichloromethane solution at room temperature furnishing the expected products in good to excellent yields (Table 2).[15,16]



Scheme 2

Table 2 Synthesis of 2-Aminobenzimidazoles from **3**

Entry	**3**	X	Ar	**6**	R	Product **7**	Yield (%)[a]
1	**3a**	Cl	4-MeC_6H_4	**6a**	*n*-Bu	**7aa**	85
2	**3b**	OMe	4-MeC_6H_4	**6a**	*n*-Bu	**7ba**	87
3	**3c**	Cl	2,6-$Me_2C_6H_3$	**6a**	*n*-Bu	**7ca**	94
4	**3d**	F	4-ClC_6H_4	**6a**	*n*-Bu	**7da**	93
5	**3d**	F	4-ClC_6H_4	**6b**	Et	**7db**	86
6	**3d**	F	4-ClC_6H_4	**6c**	*t*-Bu	**7dc**	89
7	**3d**	F	4-ClC_6H_4	**6d**	Ph	**7dd**	69
8	**3c**	Cl	2,6-$Me_2C_6H_3$	**6b**	Et	**7cb**	90
9	**3a**	Cl	4-MeC_6H_4	**6b**	Et	**7ab**	92
10	**3e**	Br	4-MeC_6H_4	**6b**	Et	**7eb**	91
11	**3f**	Cl	2-MeC_6H_4	**6b**	Et	**7fb**	89

[a] Isolated yield.

Since variously substituted 2-aminobenzimidazoles show biological activity[17] this simple and efficient method for their formation should provide a worthwhile approach compared to the other known routes.

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(10) **General Procedure for the Synthesis of 3**
To a stirred suspension of Ph_3P (3275 mg, 12.5 mmol) in dry MeCN (25 mL) solid *N*-aryl-2-nitrosoaniline **1** (5 mmol) was added portionwise over 30 min under external cooling with cold water, and the mixture was stirred at r.t. overnight. The precipitated solid was filtered off, and the filtrate was concentrated under vacuum and chromatographed using hexane–EtOAc gradient elution (8:1 to 2:1). An analytically pure sample of the product was obtained by recrystallization from EtOAc–hexane.

(11) **Analytical Data for Novel Products 3**
Compound **3a**: pale yellow crystals; mp 164–167 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s, 3 H), 6.22 (d, *J* = 8.2 Hz, 1 H), 6.32 (dd, *J* = 8.2, 2.5 Hz, 1 H), 6.95 (t, *J* = 2.6 Hz, 1 H), 7.12 (s, 4 H), 7.55–7.61 (m, 7 H), 7.62–7.66 (m, 3

H), 7.73–7.78 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.3, 110.8, 117.5, 118.8, 119.2 (d, J_{CP} = 10 Hz), 120.8, 129.0 (d, J_{CP} = 12 Hz), 129.5 (d, J_{CP} = 99 Hz), 129.6, 129.7, 132.1 (d, J_{CP} = 10 Hz), 132.2 (d, J_{CP} = 2 Hz), 137.5, 139.1 (d, J_{CP} = 20 Hz), 140.0. Ms (EI): *m/z* (%) = 495 (19), 494 950), 493 (50), 492 (100), 262 (44), 183 (45). HRMS (EI): *m/z* calcd for $C_{31}H_{26}N_2{}^{31}P^{35}Cl$: 492.1522; found: 492.1529.

Compound **3b**: pale yellow crystals; mp 188–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.24 (s, 3 H), 3.55 (s, 3 H), 5.92–5.98 (m, 1 H), 6.18–6.25 (m, 1 H), 6.65–6.71 (m, 1 H), 7.08 (s, 4 H), 7.52–7.65 (m, 10 H), 7.71–7.80 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.3, 54.9, 99.9, 102.3, 117.7, 118.5 (d, J_{CP} = 9 Hz), 128.7, 128.9 (d, J_{CP} = 12 Hz), 129.6, 130.4 (d, J_{CP} = 99 Hz), 132.0, 132.1, 137.9 (d, J_{CP} = 20 Hz), 140.7, 151.5 (one C missing). MS (EI): *m/z* (%) = 490 (11), 489 (46), 488 (100), 262 (32), 183 (34). HRMS (EI): calcd for $C_{32}H_{29}N_2{}^{31}PO^{35}Cl$: 488.2018; found: 488.2014.

Compound **3c**: grey crystals; mp 183–185 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.17 (s, 6 H), 5.74 (s, 1 H), 6.18 (s, 2 H), 7.06–7.12 (m, 2 H), 7.15–7.18 (m, 2 H), 7.56–7.67 (m, 9 H), 7.77–7.83 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.9, 108.1, 115.7, 118.7 (d, J_{CP} = 10 Hz), 121.2, 125.6, 128.2, 129.0 (d, J_{CP} = 12 Hz), 129.9 (d, J_{CP} = 99 Hz), 132.1 (d, J_{CP} = 9 Hz), 132.2 (d, J_{CP} = 3 Hz), 135.4, 136.3, 139.6, 142.1 (d, J_{CP} = 20 Hz). MS (EI): *m/z* (%) = 509 (17), 508 (51), 507 (51), 506 (100), 262 (55), 183 (62). HRMS (EI): *m/z* calcd for $C_{32}H_{28}N_2{}^{31}P^{35}Cl$: 506.1679; found: 506.1678.

Compound **3d**: dark green solid; mp 131–133 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.18–6.26 (m, 2 H), 6.89 (dt, *J* = 10.8, 2.7 Hz, 1 H), 7.18–7.22 (m, 2 H), 7.27–7.30 (m, 2 H), 7.54–7.59 (m, 6 H), 7.61–7.66 (m, 3 H), 7.71–7.77 (m, 6 H), 7.85 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 101.1 (d, J_{CF} = 26 Hz), 104.9 (d, J_{CF} = 21 Hz), 118.6, 118.7 (d, J_{CP} = 19 Hz), 123.0, 129.0 (d, J_{CP} = 12 Hz), 130.5 (d, J_{CP} = 99 Hz), 132.1 (d, J_{CP} = 10 Hz), 135.9 (d, J_{CP} = 2 Hz), 136.9 (d, J_{CF} = 10 Hz), 137.0 (d, J_{CF} = 11 Hz), 142.0, 154.6 (d, J_{CF} = 232). MS (EI): *m/z* (%) = 499 (13), 498 (44), 497 (43), 496 (100), 262 (58), 183 (55). HRMS (EI): *m/z* calcd for $C_{30}H_{23}N_2{}^{31}P^{35}ClF$: 496.1271; found: 496.1270.

Compound **3e**: grey crystals; mp 191–193 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s, 3 H), 6.18 (d, *J* = 8.2 Hz, 1 H), 6.43 (dd, *J* = 8.2, 2.5 Hz, 1 H), 7.06 (br s, 1 H), 7.09–7.15 (m, 4 H), 7.54–7.61 (m, 7 H), 7.63–7.66 (m, 3 H), 7.72–7.79 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.3, 108.4, 135.5, 118.8, 119.8 (d, J_{CP} = 10 Hz), 120.4, 129.0 (d, J_{CP} = 11 Hz), 129.5 (d, J_{CP} = 96 Hz), 129.7, 129.8, 132.1 (d, J_{CP} = 8 Hz), 132.2 (d, J_{CP} = 2 Hz), 138.0, 139.5 (d, J_{CP} = 21 Hz), 140.0. MS (EI): *m/z* (%) = 539 (39), 538 (100), 537 (49), 536 (98), 262 (61), 183 (58). HRMS (EI): *m/z* calcd for $C_{31}H_{26}N_2{}^{31}P^{79}Br$: 536.1017; found: 536.1016.

Compound **3f**: pale green crystals; mp 172–173 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.24 (s, 3 H), 6.24 (d, *J* = 8.3 Hz, 1 H), 6.34 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.88–6.92 (m, 2 H), 7.18–7.26 (m, 2 H), 7.34–7.37 (m, 1 H), 7.54 (s, 1 H), 7.56–7.61 (m, 6 H), 7.64–7.68 (m, 3 H), 7.73–7.80 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.6, 110.6, 117.4, 117.6, 119.1 (d, J_{CP} = 10 Hz), 120.9, 121.2, 126.7, 127.6, 129.0 (d, J_{CP} = 13 Hz), 129.9 (d, J_{CP} = 99 Hz), 130.0, 132.0 (d, J_{CP} = 10 Hz), 132.3 (d, J_{CP} = 3 Hz), 137.5, 138.9 (d, J_{CP} = 20 Hz), 140.6. MS (EI): *m/z* (%) = 494 (46), 493 (46), 492 (100), 262 (51), 183 (58). HRMS (EI): *m/z* calcd for $C_{31}H_{26}N_2{}^{31}P^{35}Cl$: 492.1522; found: 492.1513.

Compound **3g**: pale yellow crystals; mp 150–151 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.26 (dd, *J* = 8.3, 1.0 Hz, 1 H), 6.43 (dd, *J* = 8.3, 2.5 Hz, 1 H), 7.04 (t, *J* = 2.7 Hz, 1 H), 7.16–7.19 (m, 2 H), 7.27–7.30 (m, 2 H), 7.54–7.59 (m, 6 H), 7.61–7.66 (m, 3 H), 7.71–7.76 (m, 6 H), 7.81 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 113.8, 118.7, 119.3, 119.9 (d, J_{CP} = 10 Hz), 120.5, 123.0, 128.9, 129.0 (d, J_{CP} = 12 Hz), 129.5 (d, J_{CP} = 99 Hz), 132.1 (d, J_{CP} = 10 Hz), 132.2 (d, J_{CP} = 3 Hz), 137.5 (d, J_{CP} = 20 Hz), 139.1, 142.2. MS (EI): *m/z* (%) = 516 (20), 515 (32), 514 (74), 513 (51), 512 (100), 262 (63), 183 (64). HRMS (EI): *m/z* calcd for $C_{30}H_{23}N_2{}^{31}P^{35}Cl_2$: 512.0976; found: 512.0974.

Compound **3h**: yellow crystals; mp 185–186 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.25 (s, 3 H), 6.38 (d, *J* = 8.1 Hz, 1 H), 6,65 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.09–7.11 (m, 2 H), 7.19–7.20 (m, 3 H), 7.31–7.37 (m, 3 H), 7.44–7.46 (m, 2 H), 7.55–7.61 (m, 7 H), 7.64–7.67 (m, 3 H), 7.76–7.84 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 117.4, 118.7, 125.8, 126.2 126.4, 127.1, 128.4, 128.5 (d, J_{CP} = 12 Hz), 128.8 (d, J_{CP} = 11 Hz), 129.1 (d, J_{CP} = 99 Hz), 129.7, 130.3, 131.8 (d, J_{CP} = 3 Hz), 132.1 (d, J_{CP} = 10 Hz), 132.5–133.0 (br signal), 141.4; some carbons not observed. MS (EI): *m/z* (%) = 535 (52), 534 (100), 262 (33), 183 (30). HRMS (EI): *m/z* calcd for $C_{37}H_{31}N_2{}^{31}P$: 534.2225; found: 524.2215.

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(15) **General Procedure for the Synthesis of 7**

The requisite **3** (1 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and isocyanate **6** (1.1 mmol) was added in one portion. The reaction flask was stoppered and stirred overnight. After completion (TLC control) the solvent was evaporated, and the residue was subjected to column chromatography (SiO_2, hexane–EtOAc, 1:1). Analytically pure samples of solid products were obtained by recrystallization from hexane–EtOAc.

(16) **Analytical Data for Novel Products 7**

Compound **7aa**: brown oil ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.87 (t, *J* = 7.4 Hz, 3 H), 1.26–1.35 (m, 2 H), 1.52–1.59 (m, 2 H), 2.42 (s, 3 H), 3.29–3.34 (m, 2 H), 6.34 (t, *J* = 5.6 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 1 H), 7.00 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.24 (d, *J* = 8.3 Hz, 1 H), 7.32–7.35 (m, 2 H), 7.41–7.45 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.7, 19.5, 20.7, 31.1, 42.1, 107.1, 115.9, 120.7, 122.6, 126.8, 130.7, 131.4, 136.4, 138.2, 141.9, 155.1. MS (EI): *m/z* (%) = 315 (31), 314 (22), 313 (88), 286 (4), 285 (4), 284 (14), 273 (18), 272 (28), 271 (59), 270 (61), 259 (35), 258 (35), 257 (100), 256 (58). HRMS (EI): *m/z* calcd for $C_{18}H_{20}N_3{}^{35}Cl$: 313.1346; found: 313.1351.

Compound **7ba**: orange solid; mp 183–184 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.88 (t, *J* = 7.4 Hz, 3 H), 1.26–1.35 (m, 2 H), 1.52–1.58 (m, 2 H), 2.41 (s, 3 H), 3.29–3.30 (m, 2 H), 3.64 (s, 3 H), 5.95 (t, *J* = 5.6 Hz, 1 H), 6.36 (d, *J* = 2.3 Hz, 1 H), 6.61 (dd, *J* = 8.4, 2.3 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 7.30–7.34 (m, 2 H), 7.41–7.44 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.7, 19.5, 20.7, 31.1, 42.2, 55.5, 93.4, 107.8, 115.3, 126.7, 130.6, 132.0, 135.8, 136.9, 137.7,

153.5, 153.9. MS (EI): *m/z* (%) = 310 (43), 309 (100), 294 (18), 280 (10), 267 (28), 266 (36), 253 (47), 252 (20). HRMS (EI): *m/z* calcd for $C_{19}H_{23}O$: 309.1841; found: 309.1834.
Compound **7ca**: brown crystals; mp 91–93 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 7.4 Hz, 3 H), 1.25–1.36 (m, 2 H), 1.50–1.57 (m, 2 H), 1.90 (s, 3 H), 3.28–3.34 (m, 2 H), 6.31 (t, *J* = 5.7 Hz, 1 H), 6.40 (d, *J* = 2.1 Hz, 1 H), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 7.31 (d, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.7, 17.1, 19.4, 31.2, 41.9, 106.5, 115.9, 120.6, 122.6, 128.8, 129.4, 131.3, 135.1, 137.0, 142.2, 154.8. MS (EI): *m/z* (%) = 329 (44), 328 (34), 327 (100), 300 (7), 299 (5), 298 (20), 287 (13), 286 (19), 285 (39), 284 (41), 257 (22), 256 (22), 255 (60), 254 (10). HRMS (EI): *m/z* calcd for $C_{19}H_{22}N_3{}^{35}Cl$: 327.1502; found: 327.1503.
Compound **7da**: brown oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.89 (t, *J* = 7.2, 3 H), 1.28–1.36 (m, 2 H), 1.53–1.59 (m, 2 H), 3.26–3.32 (m, 2 H), 6.34–6.39 (m, 2 H), 6.62–6.65 (m, 1 H), 6.80–6.85 (m, 1 H), 7.23 (dd, *J* = 8.2 Hz, J_{HF} = 4.7 Hz, 1 H), 7.48–7.53 (m, 2 H), 7.66–7.70 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.7, 19.5, 31.1, 42.2, 95.0 (d, J_{CF} = 29 Hz), 107.7 (d, J_{CF} = 24 Hz), 115.2 (d, J_{CF} = 9 Hz), 128.9, 130.2, 133.0, 133.2, 135.3 (d, J_{CF} = 13 Hz), 139.3, 154.8, 156.8 (d, J_{CF} = 231 Hz). MS (EI): *m/z* (%) = 319 (40), 318 (30), 317 (97), 290 (5), 289 (4), 288 (15), 277 (21), 276 (31), 275 (64), 274 (66), 263 (40), 262 (40), 261 (100), 260 (64), 239 (10), 238 (29). HRMS (EI): *m/z* calcd for $C_{17}H_{17}N_3{}^{35}ClF$: 317.1095; found: 317.1096.
Compound **7db**: colorless crystals; mp 146 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 3.33 (q, overlapped by H_2O peak, 2 H), 6.39 (t, *J* = 5.7 Hz, 1 H), 6.65 (dd, *J* = 2.5 Hz, J_{HF} = 9.0 Hz, 1 H), 6.83 (ddd, *J* = 8.5, 2.5 Hz, J_{HF} = 9.0 Hz, 1 H), 7.23 (dd, *J* = 8.5 Hz, J_{HF} = 4.8 Hz, 1 H), 7.50–7.53 (m, 2 H), 7.66–7.69 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.3, 37.8, 95.6 (d, J_{CF} = 28 Hz), 108.2 (d, J_{CF} = 24 Hz), 115.8 (d, J_{CF} = 10 Hz), 129.4, 130.7, 133.4, 133.7, 135.7 (d, J_{CF} = 12 Hz), 139.8, 155.1 (d, J_{CF} = 2 Hz), 157.3 (d, J_{CF} = 231 Hz). MS (EI): *m/z* (%) = 291 (32), 290 (20), 289 (100), 263 (23), 262 (24), 261 (70), 260 (42), 238 (19), 225 (42). HRMS (EI): *m/z* calcd for $C_{15}H_{13}N_3{}^{35}ClF$: 289.0782; found: 289.0782.
Compound **7dc**: orange oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.41 (s, 9 H), 5.57 (s, 1 H), 6.66 (dd, *J* = 2.5 Hz, J_{HF} = 9.1 Hz, 1 H), 6.84 (ddd, *J* = 8.6, 2.5 Hz, J_{HF} = 10.1 Hz, 1 H), 7.28 (dd, *J* = 8.6 Hz, J_{HF} = 4.7 Hz, 1 H), 7.49–7.53 (m, 2 H), 7.65–7.68 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.6, 51.5, 95.1 (d, J_{CF} = 28 Hz), 107.8 (d, J_{CF} = 24 Hz), 115.7 (d, J_{CF} = 9 Hz), 128.8, 130.2, 132.7, 133.6, 134.5 (d, J_{CF} = 13 Hz), 139.2, 152.9 (d, J_{CF} = 2 Hz), 157.0 (d, J_{CF} = 232 Hz). MS (EI): *m/z* (%) = 319 (17), 318 (12), 317 (39), 263 (46), 262 (40), 261 (100), 260 (45), 226 (16), 225 (32). HRMS (EI): *m/z* calcd for $C_{17}H_{17}N_3{}^{35}ClF$: 317.1095; found: 317.1087.
Compound **7dd**: white solid; mp 164–166 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.76 (dd, *J* = 2.4 Hz, J_{HF} = 8.9 Hz, 1 H), 6.93–6.99 (m, 2 H), 7.27–7.31 (m, 2 H), 7.44 (dd, *J* = 8.6 Hz, J_{HF} = 4.9 Hz, 1 H), 7.59–7.63 (m, 2 H), 7.69–7.73 (m, 2 H), 7.76–7.79 (m, 2 H), 8.71 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 95.7 (d, J_{CF} = 29 Hz), 108.7 (d, J_{CF} = 24 Hz), 116.9 (d, J_{CF} = 10 Hz), 118.3, 121.3, 128.4, 129.4, 130.3, 133.1, 133.4, 134.6 (d, J_{CF} = 13 Hz), 138.3, 140.5, 150.4, 157.7 (d, J_{CF} = 234 Hz). MS (EI): *m/z* (%) = 339 (43), 338 (47), 337 (100), 336 (64), 323 (18), 322 (12), 321 (51). HRMS (EI): *m/z* calcd for $C_{19}H_{13}N_3{}^{35}ClF$: 337.0782; found: 337.0786.
Compound **7cb**: colorless crystals; mp 148–149 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13 (t, *J* = 7.1 Hz, 3 H), 1.90 (s, 6 H), 3.35 (q, *J* = 7.1 Hz, 2 H), 6.32 (t, *J* = 5.7 Hz, 1 H), 6.42 (d, *J* = 2.2 Hz, 1 H), 7.01 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.30–7.33 (m, 2 H), 7.40 (dd, *J* = 6.9, 8.2 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.0, 17.1, 37.1, 106.6, 116.0, 120.7, 122.7, 128.9, 129.5, 131.3, 135.0, 137.0, 142.2, 154.7. MS (EI): *m/z* (%) = 301 (35), 300 (23), 299 (100), 284 (19), 271 (20), 257 (18), 256 (17), 255 (49), 228 (23). HRMS (EI): *m/z* calcd for $C_{17}H_{18}N_3{}^{35}Cl$: 299.1189; found: 299.1194.
Compound **7ab**: yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.42 (s, 3 H), 3.36 (q, *J* = 7.1 Hz, 2 H), 6.36 (t, *J* = 5.6 Hz, 1 H), 6.72 (d, *J* = 2.2 Hz, 1 H), 7.01 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.33–7.36 (m, 2 H), 7.42–7.45 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 20.7, 37.3, 107.2, 116.0, 120.8, 122.7, 126.8, 130.7, 131.4, 136.4, 138.2, 141.9, 155.0. MS (EI): *m/z* (%) = 287 (37), 286 (24), 285 (100), 271 (20), 259 (22), 258 (27), 257 (68), 256 (53), 241 (27). HRMS (EI): *m/z* calcd for $C_{16}H_{16}N_3{}^{35}Cl$: 285.1033; found: 285.1021.
Compound **7eb**: grey oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.42 (s, 3 H), 3.35 (q, *J* = 7.1 Hz, 2 H), 6.38 (t, *J* = 5.4 Hz, 1 H), 6.84 (d, *J* = 2.0 Hz, 1 H), 7.12 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 7.33–7.36 (m, 2 H), 7.41–7.45 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.4, 21.2, 37.8, 110.3, 110.7, 117.1, 124.0, 127.3, 131.2, 131.9, 137.3, 138.7, 142.7, 155.3. MS (EI): *m/z* (%) = 332 (19), 331 (98), 330 (27), 329 (100), 303 (52), 302 (48), 301 (45), 287 (21), 285 (24). HRMS (EI): *m/z* calcd for $C_{16}H_{16}N_3{}^{79}Br$: 329.0528; found: 329.0530.
Compound **7fb**: grey oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.96 (s, 3 H), 3.34 (q, *J* = 7.2 Hz, 2 H), 6.31 (t, *J* = 5.5 Hz, 1 H), 6.48 (d, *J* = 2.0 Hz, 1 H), 7.00 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 7.32–7.35 (m, 1 H), 7.42–7.46 (m, 2 H), 7.50–7.52 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.0, 17.0, 37.2, 106.9, 115.9, 120.7, 122.6, 127.7, 128.9, 129.7, 131.7, 132.5, 136.2, 136.5, 142.0, 155.1. MS (EI): *m/z* (%) = 287 (34), 286 (21), 285 (100), 270 (17), 259 (18), 258 (22), 257 (55), 256 (42), 241 (28). HRMS (EI): *m/z* calcd for $C_{16}H_{16}N_3{}^{35}Cl$: 285.1033; found: 285.1032.

(17) For recent development, see: (a) Correa, R. G.; Khan, P. M.; Askari, N.; Zai, D.; Gerlic, M.; Brown, B.; Magnuson, G.; Spreafico, R.; Albani, S.; Sergienko, E.; Diaz, P. W.; Roth, G. P.; Reed, J. P. *Chem. Biol. (Oxford, UK)* **2011**, *18*, 825. (b) Cook, B. N.; Bentzien, J.; White, A.; Nemoto, P. A.; Wanga, J.; Mana, C. C.; Soleymanzadeh, F.; Khine, H. H.; Kashem, M. A.; Kugler, S. Z. Jr.; Wolak, J. P.; Roth, G. P.; Lombaert, S.; Pullen, S. S.; Takahashi, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 773. (c) Das, P.; Kumar, C. K.; Kumar, K. N.; Innus, M.; Iqbal, J.; Srinivas, N. *Tetrahedron Lett.* **2008**, *49*, 992. (d) Zhu, J.; Wu, C. F.; Li, X.; Wu, G. S.; Xie, S.; Hua, Q.-N.; Deng, Z.; Zhu, M. X.; Luo, H.-R.; Hong, X. *Bioorg. Med. Chem.* **2013**, *21*, 4218. (e) Hranjec, M.; Sovcić, I.; Ratkaj, I.; Pavlović, G.; Ilić, N.; Valjalo, L.; Pavelić, K.; Pavelić, S. K.; Karminski-Zamola, G. *Eur. J. Med. Chem.* **2013**, 111.

