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Simple Synthesis of Dimethyl Nitrobenzhydrylphosphonates and Heteroarylnitroarylacetonitriles via Vicarious Nucleophilic Substitution (VNS) Reaction

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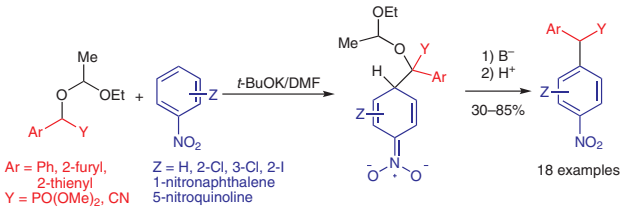

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Abstract Acetals of dimethyl phenyl- and heteroaryl-α-hydroxymethanephosphonates were deprotonated to generate carbanions, which enter the vicarious nucleophilic substitution (VNS) of hydrogen in aromatic nitro compounds to form 4-nitrobenzhydrylphosphonates and α-heteroaryl-4-nitrobenzylphosphonates. Similarly acetals of cyanohydrins of heteroaromatic aldehydes (furfural and 2-formylthiophene) react to form heteroaryl 4-nitroarylacetonitriles. The anion of the hemiacetal of acetaldehyde is an efficient leaving group in the base-induced β-elimination step – the crucial step in the VNS reaction. The reaction selectively occurred at the *para*-position to the nitro group.

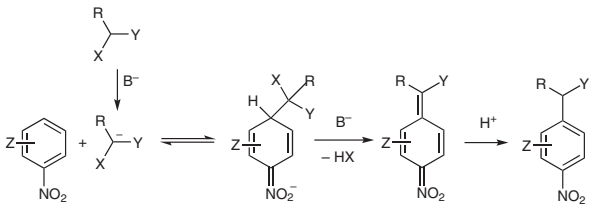
Key words arylmethanephosphonates, arylacetonitriles, carbanions, nitroarenes, acetals, vicarious nucleophilic substitution

Vicarious nucleophilic substitution (VNS) of hydrogen is presently a well-established method of introduction of carbon, nitrogen, and oxygen substituents into electron-deficient aromatic rings, particularly nitroarenes.[1] The most important and widely used variant of this process consists in the addition of α-chlorocarbanions to nitroaromatic rings to the *ortho*- and/or *para*-positions occupied by hydrogens.[2,3] Subsequent base-induced β-elimination of HCl from the formed σ^H-adduct gives products in the form of nitrobenzylic carbanions isolated upon protonation. Since α-chlorocarbanions are very unstable it was shown that carbanions containing some other leaving groups such as methoxy, phenoxy, phenylthio, *N*,*N*-dialkyldithiocarbamoyl are in some cases more convenient starting materials in the VNS reaction.[4,5] VNS is an efficient tool for replacement of hydrogen in aromatic rings with carbon substituents, hence can be considered as an umpolung and complementary to the Friedel–Crafts reaction that cannot be applied to nitroarenes (Scheme 1).

Dialkyl benzyl- and benzhydrylphosphonates are widely used in agrochemistry and pharmacy, since development of simple synthesis of this class of compounds is of great interest.[6]

There are a few ways of synthesis of dialkyl benzhydrylphosphonates: typical Michaelis–Becker and Arbuzov reactions of benzhydryl halides with dialkyl or trialkyl phosphites,[7] Friedel–Crafts type reaction of α-chlorobenzylphosphonates,[8] and Pd-catalyzed nucleophilic substitution of bromide in bromobenzenes by dialkyl benzylphosphonate carbanions.[9] Earlier we have reported VNS in nitrobenzenes by carbanion of dialkyl α-chlorobenzylphosphonates[2] that was confirmed in other laboratories[10] and oxidative substitution (ONSH) in nitrobenzenes by carbanion of dialkylbenzylphosphonate.[11] Both of these reactions gave dialkyl nitrobenzhydrylphosphonates.

In 2019, an interesting paper describing synthesis of diarylmethanephosphonates via BF_3-catalyzed reactions of trimethylsilyl-protected diethyl α-hydroxybenzyl phosphonates, generated in situ from aromatic aldehydes and triethyl phosphite with electron-rich arenes was published by Korean chemists.[12] This reaction is a classic example of the Friedel–Crafts reaction.



Scheme 1 General scheme of the VNS reaction

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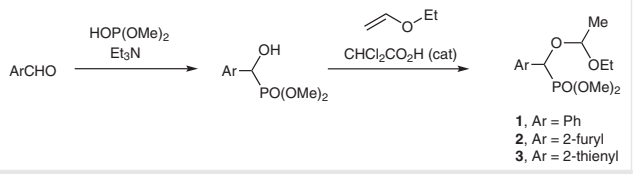
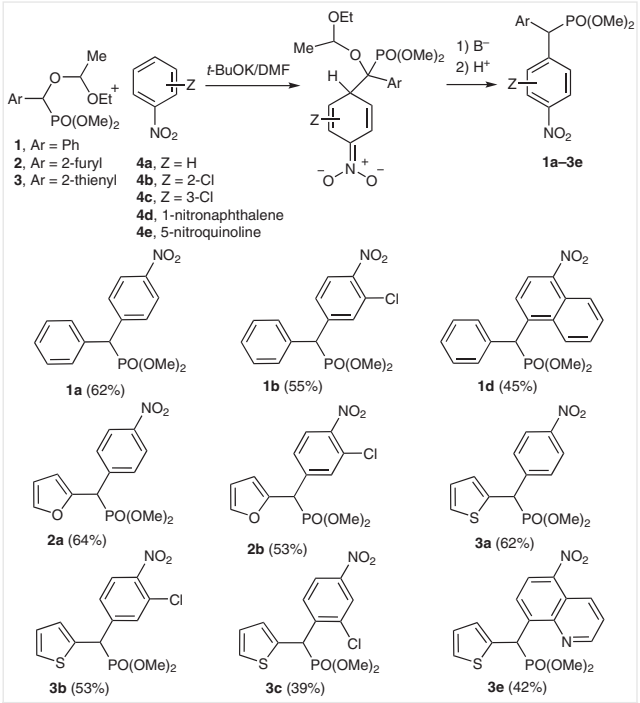
Similarly, diarylacetonitriles are versatile intermediates in organic synthesis, particularly as pharmaceuticals and plant protection agents. They are usually synthesized via Friedel–Crafts reaction of α-cyanobenzylic electrophiles with arenes,[13] reactions of benzhydrylic halides with cyanide sources,[14] transition-metal-catalyzed reactions of aryl bromides with arylacetonitriles carbanions,[15] or S_NAr substitution of halogen in *ortho*- and *para*-halonitroarenes by phenylacetonitrile carbanions.[16] Surprisingly, arylheteroarylacetonitriles are scarcely mentioned in literature. Phenylpyridyl[17] and phenylquinazolyl[18] acetonitriles were obtained via substitution of bromine in these azine rings by reaction with phenylacetonitrile carbanion. A series of diheteroarylacetonitriles have been obtained via reductive transformation of 1,1-diheteroaryl-2-nitroethanes.[19] On the other hand arylfuryl and arylthienylacetonitriles were not described. Some years ago we have reported that nitrodiarylacetonitriles are efficiently synthesized via VNS reaction of carbanions of α-methoxy- and α-phenoxyphenylacetonitriles with nitroarenes.[5] Recently, we have presented a simple synthesis of *p*-nitrodiarylacetonitriles via VNS reaction of carbanions generated from readily available cyanohydrins of aromatic aldehydes protected in the form of acetals in the reaction with ethyl vinyl ether.[20] Observation that a hemiacetal group can be eliminated in base-induced β-elimination prompted us to attempt VNS reaction in nitroarenes by carbanions of readily available dimethyl α-hydroxybenzylphosphonates O-protected in a form of acetals and expand this approach to the synthesis of heteroarylnitroarylacetonitriles.

The starting dimethyl aryl-α-hydroxymethanephosphonates were obtained via base-catalyzed addition of dimethyl phosphite to benzaldehyde, furfural, and 2-formylthiophene following the known procedure.[21] Protection of the hydroxy group in these hydroxyarylmethylphosphonates in the reaction with ethyl vinyl ether was not reported in the literature. We have found that this protection proceeds smoothly upon treatment of these α-hydroxyphosphonates and ethyl vinyl ether in diethyl ether catalyzed by dichloroacetic acid (Scheme 2). Desired protected phosphonates **1**–**3** were purified by column chromatography and were obtained in good yields as mixtures of two diastereoisomers.



Scheme 2 Synthesis of protected of α-hydroxyarylmethanephosphonates

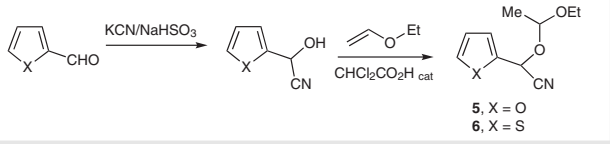
The first experiments of the VNS reaction of phosphonate **1** with nitrobenzene (**4a**) were carried out under conditions commonly used for this reaction. Addition of a solution of equimolar amounts of phosphonate **1** and nitrobenzene (**4a**) in DMF to *t*-BuOK (3 molar excess) in DMF at –10 °C resulted in an intense purple coloration of the reaction mixture. After stirring for 30 minutes, the reaction mixture was quenched with acidified water and the product was isolated and purified by column chromatography. The expected product dimethyl 4-nitrobenzhydrylphosphonate (**1a**) was isolated in 62% yield. Under similar conditions the phosphonates **2** and **3** were reacted with nitroarenes to give expected esters of diarylmethylphosphonic acids **1a–3e**. The products are presented in Scheme 3.



Scheme 3 Synthesis of aryl/heteroarylmethanephosphonates

Yields of the nitroarylheteroarylmethane phosphonates **1a–3e** are only moderate because in cases of every reactions some amounts of unidentified and tarry materials were formed. The lower yields are probably due to a steric hindrance in the σ^H-adduct caused by the bulky carbanions of **1–3**.

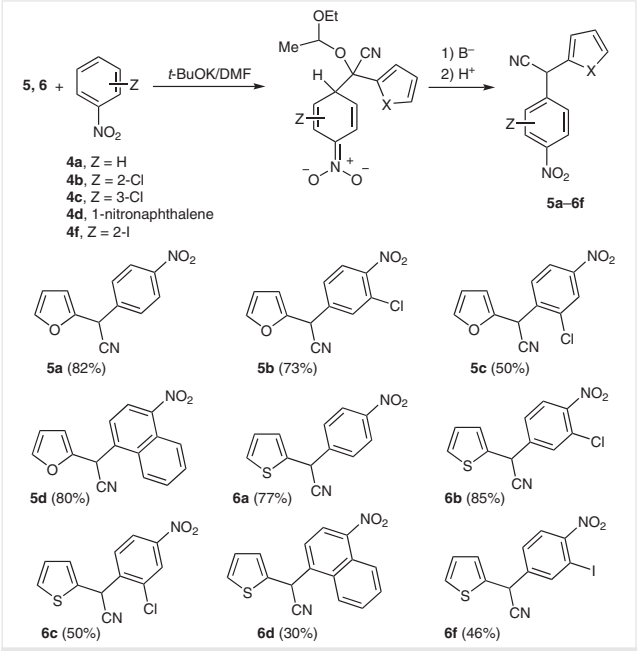
Cyanohydrins of furfural and 2-formylthiophene were prepared by the reaction of the aldehydes with sodium cyanide in the presence of $NaHSO_3$ following the known procedure.[22] Protection of these cyanohydrins in the reaction with ethyl vinyl ether was not reported. Acetal of the furfural cyanohydrin **5** was synthesized via reaction of the cyanohydrin with ethyl vinyl ether catalyzed by dichloroacetic acid. In the same manner, acetal **6** of the cyanohydrin of 2-formylthiophene was prepared (Scheme 4). The protected cyanohydrins of furfural **5** and 2-formylthiophene **6** were purified by column chromatography and obtained as a mixture of two diastereoisomers in about a 1:1 ratio.



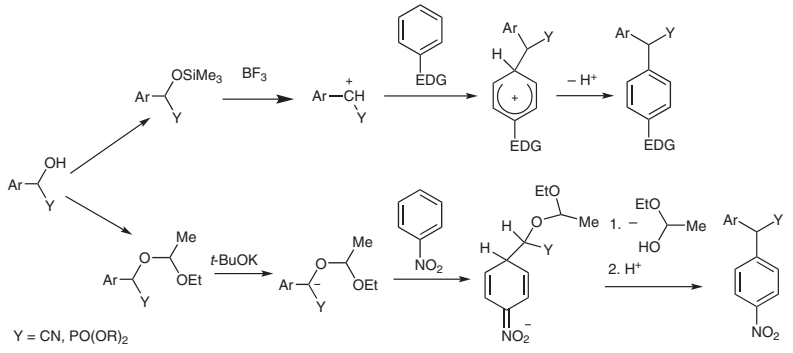
Scheme 4 Synthesis of cyanohydrin acetals

The preliminary reaction of **5** with nitrobenzene (**4a**) was carried out under the conditions commonly used for the VNS reaction by the addition of equimolar mixture of the reagents dissolved in DMF to a solution of potassium *tert*-butoxide (three molar excess) in DMF at –10 °C. The addition resulted in strong red-violet (purple) coloration of the mixture characteristic for *para*-nitrobenzyl carbanions. After stirring for 30 minutes, the mixture was poured into dilute HCl, and the product was isolated and purified by column chromatography. The expected fur-2-yl-(4-nitrophenyl)acetonitrile (**5a**) was obtained in a good yield of 82%. Since bulky sterically demanding carbanion of **5** does not add at the *ortho*-position in relation to the nitro group the substitution proceeds selectively at the *para*-position, so no isomers are formed. The mechanism of this reaction consist in the formation of the σ^H-adduct that undergoes base-induced elimination of acetaldehyde hemiacetal to form carbanion of the final product. Under similar conditions **6** was reacted with a variety of substituted nitroarenes **4**. Due to bulkiness of this carbanion only nitroarenes unsubstituted in the *para*-position to the nitro group entered the VNS reaction with **5** and **6**. Under similar conditions VNS reaction of thienyl derivative **6** with nitroarenes was performed. Also in this case the bulky carbanion entered the substitution selectively in the *para*-position to the nitro group giving (*p*-nitroaryl)thien-2-ylacetonitriles **6a–d**,**f**. The results of these experiments are shown in Scheme 5. The heteroarylnitroarylacetonitriles are obtained via the VNS reaction of the protected cyanohydrins in good yields.

In conclusion, we have shown that readily available acetals of α-hydroxybenzylphosphonates are deprotonated upon action of a strong base and the produced carbanions enter the VNS reaction with nitroarenes to give dimethyl nitrobenzhydrylphosphonates and α-heteroaryl-4-nitrobenzyl phosphonates as the final products. The presented results offer a general and versatile way to dimethyl nitrobenzhydryl- and α-(nitroaryl)-α-(heteroaryl)methanephosphonates. Similarly, deprotonation of protected cyanohydrins of heterocyclic aldehydes followed by the VNS reaction of the generated carbanions with nitroarenes produced heteroarylnitroarylacetonitriles. These results and that reported earlier[20] can be considered analogous and complementary to the recently reported[12,23] introduction of such substituents into electron-rich arenes via Friedel–Crafts reaction (Scheme 6). Complementary because they offer possibility of introduction of α-phosphorylbenzyl and α-cyanobenzyl substituents into electron-deficient nitroaromatic rings that is not possible via Friedel–Crafts reaction.



Scheme 5 Synthesis of heteroarylnitroarylacetonitriles



Scheme 6 Similarity and umpolung of the VNS and Friedel–Crafts reactions

IR spectra were recorded on JASCO FT/IR-6200 in KBr or film after evaporation from CH_2Cl_2. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 or Varian VNMR S500 (both 500 MHz for ^1H and 125 MHz for ^{13}C spectra) instruments at 298 K. Chemical shifts are expressed in parts per million (ppm) referred to TMS, coupling constants in hertz (Hz). Electron impact mass spectra (EI, 70 eV) were obtained on AutoSpec Premier spectrometer. Electrospray mass spectra (ESI) were obtained on 4000 Q-TRAP and SYNAPT G2-S HDMS. Silica gel (Merck 60, 230–400 mesh) was used for column chromatography (CC). Hexane/EtOAc mixtures were used for elution. TLC analyses were performed on Merck Kieselgel 60 F_{254} Alufolien with hexane/EtOAc mixtures. All reagents and solvents were of reagent grade or purified according to standard methods before use. All reactions were run under argon atmosphere. The starting dimethyl aryl-α-hydroxymethanephosphonates were obtained via base-catalyzed addition of dimethyl phosphite to benzaldehyde, furfural and 2-formylthiophene following the known procedure.[21] The synthesis of phosphonates **1**–**3** is described in the Supporting Information. Cyanohydrins of furfural and 2-formylthiophene were prepared following the known procedure.[22]

VNS Reaction; General Procedure

To a stirred solution of *t*-BuOK (3.5 mmol) in DMF (9 mL) that was cooled to –10 °C under an inert atmosphere was added a solution of nitroarene **4** (1 mmol) and phosphonate **1**–**3** or nitrile **5**,**6** (1 mmol) in DMF (1 mL). The resulting mixture turned a deep violet and was stirred for 30 min at this temperature. Then it was poured into a 2% solution of HCl (20 mL), and the mixture was extracted with EtOAc. The combined organic extracts were dried, concentrated, and the product was purified by column chromatography (hexane/EtOAc).

Dimethyl 4-Nitrobenzhydrylphosphonate (1a)

Yield: 198 mg (62%); brownish solid; mp 49–51 °C.

IR (KBr): 2954, 1596, 1520, 1493, 1453, 1348, 1254, 1183, 1111, 1054, 1030, 890, 868, 823, 750, 705, 564 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.56 (d, *J* = 10.7 Hz, 3 H), 3.62 (d, *J* = 10.8 Hz, 3 H), 4.56 (d, *J* = 25.1 Hz, 1 H), 7.26–7.40 (m, 3 H), 7.47–7.53 (m, 2 H), 7.67–7.73 (m, 2 H), 8.15–8.20 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.65 (d, *J* = 140 Hz), 53.30 (d, *J* = 7.0 Hz), 53.88 (d, *J* = 7.0 Hz), 123.80 (d, *J* = 1.5 Hz), 127.90 (d, *J* = 2.0 Hz), 129.03 (d, *J* = 1.2 Hz), 129.38 (d, *J* = 8.0 Hz), 130.26 (d, *J* = 7.9 Hz), 135.05 (d, *J* = 5.6 Hz), 144.19 (d, *J* = 5.2 Hz), 147.10.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.67.

MS (EI): *m*/*z* (%) = 321 (M^+, 31), 275 (11), 213 (26), 212 (100), 196 (18), 166 (40), 165 (53), 143 (13), 139 (8), 115 (7), 109 (16).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}NO_5P$: 321.0766; found: 321.0769.

Dimethyl 3-Chloro-4-nitrobenzhydrylphosphonate (1b)

Yield: 195 mg (55%); pale brown semisolid.

IR (film): 2954, 2852, 1591, 1528, 1494, 1475, 1454, 1349, 1254, 1183, 1054, 1031, 934, 907, 828, 768, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.56 (d, *J* = 10.8 Hz, 3 H), 3.68 (d, *J* = 10.8 Hz, 3 H), 4.48 (d, *J* = 25.1 Hz, 1 H), 7.30–7.34 (m, 1 H), 7.35–7.40 (m, 2 H), 7.46–7.50 (m, 2 H), 7.60 (ddd, *J* = 8.8, 1.7, 1.7 Hz, 1 H), 7.68 (dd, *J* = 1.7, 1.7 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.22 (d, *J* = 140 Hz), 53.30 (d, *J* = 7.0 Hz), 54.04 (d, *J* = 7.0 Hz), 125.84 (d, *J* = 1.3 Hz), 127.37, 128.12 (d, *J* = 2.0 Hz), 128.44 (d, *J* = 7.2 Hz), 129.16 (d, *J* = 1.0 Hz), 129.35 (d, *J* = 7.5 Hz), 132.60 (d, *J* = 8.1 Hz), 134.50 (d, *J* = 5.6 Hz), 143.22 (d, *J* = 5.0 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.10.

MS (EI): *m*/*z* (%) = 357 (M^+ + 2, 23), 355 (M^+, 38), 325 (7), 309 (9), 248 (43), 247 (28), 246 (100), 232 (10), 230 (25), 200 (33), 199 (26), 181 (20), 165 (69), 164 (22), 163 (26), 153 (24), 139 (10), 165 (69), 164 (22), 163 (27), 153 (24), 139 (10), 115 (12), 111 (13), 109 (29).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}ClNO_5P$: 355.0376; found: 355.0373.

Dimethyl (4-Nitronaphth-1-yl)phenylmethanephosphonate (1d)

Yield: 167 mg (45%); brown semi-solid.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.58 (d, *J* = 10.8 Hz, 3 H), 3.60 (d, *J* = 10.8 Hz, 3 H), 5.32 (d, *J* = 26.4 Hz, 1 H), 7.24–7.28 (m, 1 H), 7.30–7.35 (m, 2 H), 7.49–7.53 (m, 2 H), 7.60–7.70 (m, 2 H), 8.18 (d, *J* = 9.8 Hz, 1 H), 8.20 (d, *J* = 8.6 Hz, 1 H), 8.38 (dd, *J* = 7.8, 2.0 Hz, 1 H), 8.51 (br d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.13 (d, *J* = 140 Hz), 53.36 (d, *J* = 7.6 Hz), 53.97 (d, *J* = 7.4 Hz), 122.96 (d, *J* = 1.5 Hz), 123.70, 123.86, 125.64, 126.06 (d, *J* = 6.6 Hz), 127.82 (d, *J* = 2.7 Hz), 127.91, 128.81, 128.92 (d, *J* = 2.0 Hz), 129.51 (d, *J* = 6.9 Hz), 132.37 (d, *J* = 11.5 Hz), 135.01 (d, *J* = 6.6 Hz), 139.43 (d, *J* = 2.7 Hz), 146.54 (d, *J* = 1.5 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.62.

MS (EI): *m*/*z* (%) = 371 (M^+, 46), 325 (8), 263 (31), 262 (100), 261 (22), 245 (27), 231 (26), 216 (67), 215 (87), 203 (22).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}NO_5P$: 371.0923; found: 371.0920.

Dimethyl (Fur-2-yl)(4-nitrophenyl)methanephosphonate (2a)

Yield: 199 mg (64%); pale brown semisolid.

^1H NMR (500 MHz, CD_2Cl_2): δ = 3.62 (d, *J* = 10.6 Hz, 3 H), 3.68 (d, *J* = 11.0 Hz, 3 H), 4.73 (d, *J* = 26.2 Hz, 1 H), 6.43 (dd, *J* = 2.7, 2.0 Hz, 1 H), 6.53 (dd, *J* = 2.7, 2.6 Hz, 1 H), 7.44 (br s, 1 H), 7.62–7.66 (m, 2 H), 8.17–8.22 (m, 2 H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 44.74 (d, *J* = 130 Hz), 53.48 (d, *J* = 7.0 Hz), 53.70 (d, *J* = 6.9 Hz), 109.85 (d, *J* = 5.2 Hz), 111.20 (d, *J* = 1.6 Hz), 123.99 (d, *J* = 2.6 Hz), 130.67 (d, *J* = 6.2 Hz), 142.36 (d, *J* = 6.2 Hz), 143.15 (d, *J* = 2.3 Hz), 147.74 (d, *J* = 2.6 Hz), 148.52 (d, *J* = 3.8 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 19.48.

MS (EI): *m*/*z* (%) = 311 (M^+, 23), 203 (22), 202 (100), 186 (12), 172 (7), 156 (32), 128 (19), 127 (100), 109 (13).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}NO_6P$: 311.0559; found: 311.0560.

Dimethyl (3-Chloro-4-nitrophenyl)(fur-2-yl)methanephosphonate (2b)

Yield: 184 mg (53%); pale brown semisolid.

IR (film): 2956, 2854, 1639, 1584, 1529, 1475, 1353, 1254, 1184, 1033, 829, 743, 600 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.67 (d, *J* = 10.7 Hz, 3 H), 3.69 (d, *J* = 10.8 Hz, 1 H), 4.62 (d, *J* = 26.1 Hz, 1 H), 6.40 (m, 1 H), 5.52 (m, 1 H), 7.50 (ddd, *J* = 8.6, 1.9, 1.9 Hz, 1 H), 7.61 (dd, *J* = 1.9, 1.9 Hz, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.21 (d, *J* = 143 Hz), 53.59 (d, *J* = 7.2 Hz), 54.03 (d, *J* = 6.6 Hz), 109.82 (d, *J* = 5.4 Hz), 110.94 (d, *J* = 1.9 Hz), 125.75 (d, *J* = 2.3 Hz), 127.32 (d, *J* = 2.3 Hz), 128.45 (d, *J* = 6.5 Hz), 152.52 (d, *J* = 6.3 Hz), 140.77 (d, *J* = 6.3 Hz), 143.00 (d, *J* = 2.5 Hz), 147.20, 147.23.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.20.

MS (EI): *m*/*z* (%) = 347 (M^+ + 2, 22), 345 (M^+), 238 (45), 236 (100), 220 (13), 206 (19), 190 (41), 155 (27), 127 (24).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}ClNO_6P$: 345.0169; found: 345.0176.

Dimethyl (4-Nitrophenyl)(thien-2-yl)methanephosphonate (3a)

Yield: 203 mg (62%); brown semisolid.

IR (KBr): 3104, 2957, 1604, 1521, 1345, 1249, 1175, 1108, 1047, 1022, 884, 864, 801, 771, 719, 577, 555 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.61 (d, *J* = 10.9 Hz, 3 H), 3.67 (d, *J* = 10.8 Hz, 3 H), 4.81 (d, *J* = 25.8 Hz, 1 H), 7.01 (dd, *J* = 5.0, 3.7 Hz, 1 H), 7.24–7.29 (m, 2 H), 7.66–7.70 (m, 2 H), 8.20 (br d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.13 (d, *J* = 151 Hz), 53.65 (d, *J* = 6.3 Hz), 54.04 (d, *J* = 7.5 Hz), 123.85 (d, *J* = 1.3 Hz), 125.80 (d, *J* = 2.5 Hz), 127.30 (d, *J* = 1.3 Hz), 127.76 (d, *J* = 7.5 Hz), 130.12 (d, *J* = 7.6 Hz), 136.47 (d, *J* = 6.4 Hz), 143.60 (d, *J* = 6.5 Hz), 147.34.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.83.

MS (EI): *m*/*z* (%) = 327 (M^+, 22), 281 (3), 219 (23), 218 (100), 202 (11), 188 (7), 172 (37), 171 (40), 160 (14).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}NO_5PS$: 327.0330; found: 327.0325.

Dimethyl (3-Chloro-4-nitrophenyl)(thien-2-yl)methanephosphonate (3b)

Yield: 192 mg (53%); pale brown semisolid.

IR (film): 2955, 2852, 1591, 1526, 1475, 1351, 1254, 1183, 1053, 1033, 918, 829, 706 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (d, *J* = 3.7 Hz, 3 H), 3.68 (d, *J* = 3.6 Hz, 3 H), 4.73 (d, *J* = 25.8 Hz, 1 H), 7.02 (dd, *J* = 5.2, 3.6 Hz, 1 H), 7.25–7.29 (m, 2 H), 7.57 (ddd, *J* = 8.4, 1.8, 1.8 Hz, 1 H), 7.65 (dd, *J* = 1.8, 1.8 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.11 (d, *J* = 141 Hz), 53.64 (d, *J* = 7.5 Hz), 54.20 (d, *J* = 7.5 Hz), 125.85 (d, *J* = 2.5 Hz), 126.02 (d, *J* = 2.5 Hz), 127.38 (d, *J* = 1.8 Hz), 127.40 (d, *J* = 2.5 Hz), 127.94 (*J* = 6.3 Hz), 128.28 (d, *J* = 6.3 Hz), 132.40 (d, *J* = 6.3 Hz), 135.80 (d, *J* = 6.3 Hz), 142.63 (d, *J* = 5.0 Hz), 147.00.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.30.

MS (EI): *m*/*z* (%) = 363 (M^+ + 2, 14), 361 (M^+, 32), 254 (46), 253 (25), 252 (100), 236 (8), 222 (12), 208 (19), 206 (38), 171 (40), 159 (11), 127 (9), 109 (19).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}ClNO_5SP$ 360.9941; found: 360.9935.

Dimethyl (2-Chloro-4-nitrophenyl)(thien-2-yl)methanephosphonate (3c)

Yield: 142 mg (39%); pale brown semisolid.

IR (KBr): 3088, 2953, 1594, 1520, 1495, 1400, 1332, 1254, 1224, 1188, 1049, 1017, 878, 835, 789, 748, 702, 526 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.64 (d, *J* = 10.8 Hz, 3 H), 3.70 (d, *J* = 10.8 Hz, 3 H), 5.45 (d, *J* = 25.5 Hz, 1 H), 6.99 (dd, *J* = 5.1, 3.7 Hz, 1 H), 6.99 (dd, *J* = 5.2, 3.5 Hz, 1 H), 7.24–7.29 (m, 2 H), 8.13 (dd, *J* = 8.6, 2.1 Hz, 1 H), 8.17 (dd, *J* = 8.6, 2.1 Hz, 1 H), 8.29 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.00 (d, *J* = 142 Hz), 53.54 (d, *J* = 7.2 Hz), 54.31 (d, *J* = 7.6 Hz), 122.08 (d, *J* = 2.2 Hz), 124.80, 126.06 (d, *J* = 2.2 Hz), 127.23 (d, *J* = 2.7 Hz), 128.02 (d, *J* = 7.8 Hz), 131.56 (d, *J* = 4.4 Hz), 134.72 (d, *J* = 10.5 Hz), 135.75 (d, *J* = 6.1 Hz), 141.53 (d, *J* = 2.5 Hz), 147.33.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.30.

MS (EI): *m*/*z* (%) = 363 (32), 361 (M^+, 29), 254 (47), 252 (100), 237 (9), 208 (17), 206 (37), 171 (37), 159 (10).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}ClNO_5PS$: 360.9941; found: 360.9954.

(5-Nitroquinol-8-yl)(thien-2-yl)methanephosphonate (3e)

Yield: 158 mg (42%); pale brown solid; mp 119–121 °C.

IR (KBr): 3088, 2953, 1594, 1520, 1495, 1400, 1332, 1254, 1224, 1188, 1151, 1049, 1017, 878, 835, 789, 748, 702, 526 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.56 (d, *J* = 10.9 Hz, 3 H), 3.70 (d, *J* = 10.8 Hz, 1 H), 6.93 (d, *J* = 25.1 Hz, 1 H), 6.96 (dd, *J* = 5.0, 3.6 Hz, 1 H), 7.20 (d, *J* = 5.0 Hz, 1 H), 7.36 (br s, 1 H), 7.67 (dd, *J* = 8.8, 4.1 Hz, 1 H), 8.38 (d, *J* = 8.2 Hz, 1 H), 8.42 (dd, *J* = 8.2, 2.5 Hz, 1 H), 9.03 (dd, *J* = 8.8, 1.6 Hz, 1 H), 9.08 (dd, *J* = 4.1, 1.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.14 (d, *J* = 143 Hz), 53.32 (d, *J* = 7.5 Hz), 54.05 (d, *J* = 7.5 Hz), 121.35, 124.01, 124.40 (d, *J* = 2.5 Hz), 125.43 (d, *J* = 2.5 Hz), 127.04 (d, *J* = 2.5 Hz), 127.72 (d, *J* = 7.5 Hz), 128.42 (d, *J* = 5.0 Hz), 132.42, 137.80 (d, *J* = 5.3 Hz), 143.10 (d, *J* = 3.8 Hz), 145.13, 145.20, 150.77.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.51.

MS (EI): *m*/*z* (%) = 378 (M^+, 100), 346 (22), 316 (6), 300 (11), 270 (27), 269 (90), 238 (41), 223 (64), 222 (55), 191 (19).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}N_2O_5PS$: 378.0439; found: 378.0448.

(Fur-2-yl)(4-nitrophenyl)acetonitrile (5a)

Yield: 187 mg (82%); pale yellow crystals; mp 82–84 °C.

IR (film): 2925, 2211, 1330, 1608, 1585, 1523, 1347, 1191, 1111, 1014, 855, 737 595 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.33 (s, 1 H), 6.38–6.41 (m, 2 H), 7.41–7.43 (m, 2 H), 7.60 and 8.27 (AA′XX′, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.47, 109.34, 111.02, 116.26, 124.44, 128.75, 139.77, 144.11, 145.90, 148.11.

MS (EI): *m*/*z* (%) = 228 (M^+, 90), 211 (11), 198 (6), 182 (40), 154 (67), 153 (84), 140 (10), 127 (100), 116 (10), 106 (64), 77 (24).

(3-Chloro-4-nitrophenyl)(fur-2-yl)acetonitrile (5b)

Yield: 191 mg (73%); pale yellow crystals; mp 121–123 °C.

IR (film): 2210, 1733, 1609, 1584, 1530, 1347, 1199, 1146, 1095, 1051, 1015, 837, 747 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.27 (s, 1 H), 6.41 (dd, *J* = 3.2, 1.6 Hz, 1 H), 6.43 (br d, *J* = 3.2 Hz, 1 H), 7.44 (d, *J* = 1.6 Hz, 1 H), 7.44 (d, *J* = 1.6 Hz, 1 H), 7.47 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.61 (d, *J* = 1.9 Hz, 1 H), 7.92 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.06, 109.61, 111.10, 115.80, 126.39, 126.85, 128.18, 131.10, 138.70, 144.32, 145.31.

MS (EI): *m*/*z* (%) = 264 (M^+ + 2, 43), 262 (100), 245 (9), 227 (32), 217 (19), 216 (30), 215 (20), 204 (10), 189 (22), 188 (28), 187 (36), 181 (15), 169 (15), 153 (57), 152 (39), 141 (15), 140 (29), 127 (18), 126 (31), 125 (21), 114 (17), 106 (68), 99 (16).

HRMS (EI): *m*/*z* calcd for $C_{12}H_7ClN_2O_3$: 262.0145; found: 262.0148.

(2-Chloro-4-nitrophenyl)(fur-2-yl)acetonitrile (5c)

Yield: 130 mg (50%); pale brown oil.

IR (film): 3103, 2927, 2251, 1590, 1528, 1473, 1351, 1184, 11443, 1119, 1014, 892, 818, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.73 (s, 1 H), 6.39–6.43 (m, 2 H), 7.42 (br s, 1 H), 7.76 (d, *J* = 8.6 Hz, 1 H), 8.20 (dd, *J* = 8.6, 2.3 Hz, 1 H), 8.33 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.04, 109.94, 111.05, 115.71, 122.59, 125.31, 130.50, 134.35, 137.67, 144.19, 144.40, 148.47.

HRMS (ESI): *m*/*z* (M^+ – 1) calcd for $C_{12}H_6ClN_2O_3$: 261.0067; found: 261.0073

(Fur-2-yl)(4-nitronaphth-1-yl)acetonitrile (5d)

Yield: 222 mg (80%); yellowish crystals; mp 137–139 °C.

IR (film): 3125, 3063, 2924, 2825, 2251, 1604, 1528, 1367, 1346, 1259, 1227, 1146, 1069, 1014, 866, 824, 795, 766, 745 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 6.32 (d, *J* = 3.2 Hz, 1 H), 6.38 (br s, 1 H), 7.42 (br s, 1 H), 7.70–7.78 (m, 3 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 8.16 (d, *J* = 7.9 Hz, 1 H), 8.53 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.47, 109.81, 111.10, 116.61, 122.77, 123.15, 124.09, 125.19, 125.49, 128.61, 129.47, 131.10, 134.70, 143.82, 145.89, 147.88.

MS (EI): *m*/*z* (%) = 278 (M^+, 100), 261 (10), 249 (11), 231 (33), 221 (15), 205 (38), 204 (36), 203 (54), 177 (37), 176 (38), 165 (30), 151 (19).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{10}N_2O_3$: 278.0691; found: 278.0696.

(4-Nitrophenyl)(thien-2-yl)acetonitrile (6a)

Yield: 188 mg (77%); pale yellow crystals; mp 62–63 °C.

R (film): 3111, 3080, 2922, 2248, 1608, 1998, 1521, 1347, 1111, 1015, 852, 818, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.49 (s, 1 H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1 H), 7.12 (d, *J* = 3.7 Hz, 1 H), 7.34 (d, *J* = 5.1 Hz, 1H), 7.61 and 8.27 (AA′XX′, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.63, 117.64, 124.53, 127.27, 127.44, 127.45, 128.58, 136.39, 142.10, 148.04.

MS (EI): *m*/*z* (%) = 244 (M^+, 100), 227 (14), 216 (7), 198 (36), 197 (30), 196 (22), 171 (35), 154 (17), 127 (13), 122 (45).

HRMS (EI): *m*/*z* calcd for $C_{12}H_8N_2O_2S$: 244.0306; found: 244.0313.

(3-Chloro-4-nitrophenyl)(thien-2-yl)acetonitrile (6b)

Yield: 138 mg (85%); pale yellow solid; mp 36–38 °C.

IR (film): 2922, 2247, 1586, 1529, 1475, 1350, 1238, 1052, 884, 829, 709 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.43 (s, 1 H), 7.03 (dd, *J* = 5.1, 3.5 Hz, 1 H), 7.13 (d, *J* = 3.5 Hz, 1 H), 7.37 (d, *J* = 5.1 Hz, 1 H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.22, 117.18, 126.51, 126.67, 127.54, 127.57, 126.69, 128.27, 130.92, 135.65, 141.01, 147.77.

MS (EI): *m*/*z* (%) = 280 (M^+ + 2, 27), 278 (76, M^+), 261 (5), 243 (23), 231 (11), 213 (10), 197 (40), 196 (48), 184 (7), 170 (10), 148 (9), 122 (100), 95 (11), 75 (18).

HRMS (ESI): *m*/*z* (M^+ – 1) calcd for $C_{12}H_6ClN_2O_2S$: 276.9839; found: 276.9830.

(2-Chloro-4-nitrophenyl)(thien-2-yl)acetonitrile (6c)

Yield: 235 mg (50%); pale brown semisolid.

IR (KBr): 3102, 2249, 1523, 1471, 1351, 1118, 1046, 894, 853, 812, 738, 711 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.89 (s, 1 H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1 H), 7.15 (d, *J* = 3.6 Hz, 1 H), 7.34 (dd, *J* = 5.2, 1.1 Hz, 1 H), 7.81 (dd, *J* = 8.6, 2.3 Hz, 1 H), 8.33 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.14, 117.16, 122.77, 125.42, 127.26, 127.39, 127.75, 130.23, 134.06, 134.79, 140.00, 148.41.

MS (EI): *m*/*z* (%) = 280 (M^+ + 2, 47), 278 (100, M^+), 251 (14), 243 (33), 232 (18), 216 (14), 205 (27), 197 (31), 196 (39), 170 (13), 122 (56).

HRMS (EI): *m*/*z* calcd for $C_{12}H_7ClN_2O_2S$: 277.9917; found: 277.9920.

(4-Nitronaphth-1-yl)(thien-2-yl)acetonitrile (6d)

Yield: 88 mg (30%); pale brown semisolid.

IR (film): 3087, 2195, 1659, 1523, 1413, 1354, 1262, 1098, 808, 765, 735 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.11 (s, 1 H), 7.00 (dd, *J* = 4.8, 3.6 Hz, 1 H), 7.10 (m, 1 H), 7.31 (d, *J* = 4.7 Hz, 1 H), 7.69 (m, 1 H), 7.76 (m, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 8.18 (d, *J* = 7.8 Hz, 1 H), 8.53 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.64, 117.94, 122.82, 123.34, 124.15, 125.07, 125.58, 127.02, 127.38, 127.63, 128.66, 129.52, 130.92, 136.36, 136.73, 147.88.

MS (EI): *m*/*z* (%) = 294 (M^+, 100), 277 (14), 249 (23), 248 (28), 247 (55), 246 (52), 237 (11), 222 (17), 221 (36), 220 (13), 190 (9), 176 (11), 164 (21), 126 (25), 122 (52).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{10}N_2O_2S$: 294.0463; found: 194.0463.

(3-Iodo-4-nitrophenyl)(thien-2-yl)acetonitrile (6f)

Yield: 160 mg (46%); pale brown solid; mp 95–97 °C.

IR (KBr): 3090, 2247, 1581, 1526, 1348, 1035, 851, 822, 708 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.39 (s, 1 H), 7.03 (dd, *J* = 4.9, 3.3 Hz, 1 H), 7.12 (d, *J* = 3.3 Hz, 1 H), 7.36 (d, *J* = 4.9 Hz, 1 H), 7.55 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 1.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.86, 87.18, 117.21, 126.08, 127.47, 127.54, 127.62, 128.19, 135.84, 140.79, 140.88, 152.99.

MS (EI): *m*/*z* (%) = 370 (M^+, 99), 324 (6), 269 (9), 260 (11), 244 (100), 227 (14), 198 (51), 197 (64), 196 (60), 171 (50), 154 (18), 122 (82).

HRMS (EI): *m*/*z* calcd for $C_{12}H_7IN_2O_2S$: 369.9273; found: 369.9279.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707230.

References

(1) (a) Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, 3495. (b) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (c) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631. (d) Mąkosza, M. *Chem. Soc. Rev.* **2010**, *39*, 2855. (e) Mąkosza, M. *Synthesis* **2017**, *49*, 3247. (f) Loska R., Mąkosza M.; *Synthesis* **2020**, 52: in press; DOI: 10.1055/s-0040-1707149.

(2) Mąkosza, M.; Goliński, J. *Angew. Chem. Int. Ed.* **1982**, *21*, 451.

(3) (a) Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488. (b) Brześkiewicz, J.; Loska, R.; Mąkosza, M. *J. Org. Chem.* **2018**, *83*, 8499.

(4) (a) Mąkosza, M.; Winiarski, J. *Chem. Lett.* **1984**, *13*, 1623. (b) Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, 203.

(5) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.

(6) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.

(7) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. *Chem. Rev.* **2011**, *111*, 7981.

(8) Pallikonda, G.; Chakravarty, M. *Eur. J. Org. Chem.* **2013**, 944.

(9) Montel, S.; Raffier, L.; He, Y. Y.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 1446.

(10) (a) Lawrence, N. J.; Liddle, J.; Jackson, D. A. *Tetrahedron Lett.* **1995**, *36*, 8477. (b) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 41.
(11) (a) Mąkosza, M.; Sulikowski, D. *Synlett* **2010**, 1666. (b) Mąkosza, M.; Sulikowski, D. *J. Org. Chem.* **2009**, *74*, 3827.
(12) Prasad, S. S.; Singh, D. K.; Kim, I. *J. Org. Chem.* **2019**, *84*, 6323.
(13) (a) Sisido, K.; Nozaki, H.; Nozaki, M.; Okano, K. *J. Org. Chem.* **1954**, *19*, 1699. (b) Sumi, T.; Goseki, R.; Otsuka, H. *Chem. Commun.* **2017**, *53*, 11885.
(14) (a) Chen, G.; Wang, Z.; Wu, J.; Ding, K. L. *Org. Lett.* **2008**, *10*, 4573. (b) Theerthagiri, P.; Lalitha, A. *Tetrahedron Lett.* **2012**, *53*, 5535.
(15) Nambo, M.; Yar, M.; Smith, J. D.; Crudden, C. M. *Org. Lett.* **2015**, *17*, 50.
(16) Mąkosza, M.; Jagusztyn-Grochowska, M.; Ludwikow, M.; Jawdosiuk, M. *Tetrahedron* **1974**, *30*, 3723.
(17) (a) Hermann, C. K. F.; Sachdeva, Y. P.; Wolfe, J. F. *J. Heterocycl. Chem.* **1987**, *24*, 1061. (b) Cherng, Y.-J. *Tetrahedron* **2002**, *58*, 4931.
(18) Yin, Z.; Zhang, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1364.
(19) Temelli, B.; Unaleroglu, C. *Synthesis* **2014**, *46*, 1407.
(20) Rad, N.; Mąkosza, M. *Eur. J. Org. Chem.* **2018**, 376.
(21) Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385.
(22) Mąkosza, M.; Goetzen, T. *Org. Prep. Proced. Int.* **1973**, *5*, 203.
(23) Singh, D. K.; Prasad, S. S.; Kim, J.; Kim, I. *Org. Chem. Front.* **2019**, *6*, 669.