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Convenient Microwave-Assisted Synthesis of 5-Functionalized 1,2,4-Triazolium Ylides Starting from *N*′,*N*′-Disubstituted Carbohydrazonamides

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5-Functionalized 1,2,4-triazolium ylides have been prepared in good yields and in very short reaction times by reacting *N*′,*N*′-disubstituted carbohydrazonamides with 1,1′-carbonylbis(1,2,4-triazole), 1,1′-thiocarbonyldiimidazole or diphenyl *N*-cyanimidocarbonate under microwave irradiation.

Introduction

The steadily increasing number of novel drug targets demands the rapid synthesis and modification of biologically active compounds. Of the methods used in drug design, microwave-assisted synthesis represents a promising method to meet these requirements.[1] Microwave irradiation often leads to substantial reductions in reaction times and to high yields.[1] In addition, several reactions that do not occur by conventional heating can be conducted under microwave irradiation. To the best of our knowledge the microwave-assisted synthesis of heterocyclic betaines has not been previously reported. Whereas syndnonimines, such as Molsidomine, are well-known nitric oxide donors, 1,1-dialkyl-5-oxo-1,2,4-triazolium ylides **3** have been described as herbicides and fungicides (Figure 1).[2,3] Interestingly, only one publication refers to the related 5-thioxo- and 5-tosylimino derivatives.[4] Relatively few synthetic strategies exist for the preparation of 1,1-dialkyl-5-oxo-1,2,4-triazolium ylides **3**.[3–6] The known methods are multistep syntheses or require the use of phosgene.[3–6] Commonly, the yields are only low-to-moderate and relatively long reaction times are necessary.[4–6] 1,1-Dialkyl-5-oxo-1,2,4-triazolium ylides **3** have already been synthesized by the treatment of phenyl *N*-(chlorocarbonyl)-1-chlorocarbonimidate with 1,1-dialkylhydrazines (four examples) and by carbonylation of amidrazones with phosgene or chloroformates in the presence of a tertiary amine.[4,6] Another strategy utilizes *N*-methoxycarbonyl-substituted thiocarbamates and 1,1-disubstituted hydrazines as starting materials, whereas Takahashi et al. synthesized two 1,1-dialkyl-5-oxo-1,2,4-triazolium ylides **3** by treating *N*-(α-chlorobenzylidene)carbamoyl chloride with 1,1-dimethylhydrazine.[3,5] A literature search revealed that only one 1,1-dialkyl-5-thioxo-1,2,4-triazolium ylide **4** has previously been described. This compound was prepared in only 24% yield by the treatment of phenyl N^3,N^3-dimethylcarbazimidate with thiophosgene in benzene.[4] The reaction of N^3,N^3-dimethylcarbazimidate with *N*-(*p*-tolylsulfonyl)isocyanide dichloride furnished an *N*-tosylimino derivative in 60% yield.[4] However, no synthetic protocol is given for the preparation. Interestingly, the related 5-cyanimino-functionalized 1,2,4-triazolium ylides **5** have not been described before. We now report the synthesis of various 5-functionalized 1,2,4-triazolium ylides **3**–**5** by the treatment of *N*′,*N*′-disubstituted carbohydrazonamides **2** with diphenyl *N*-cyanimidocarbonate, 1,1′-carbonylbis(1,2,4-triazole) and 1,1′-thiocarbonyldiimidazole under microwave irradiation.

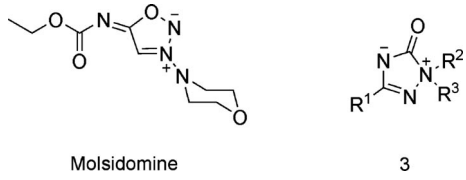

Figure 1. Heterocyclic betaines Molsidomine and **3**.

Results and Discussion

Substrates **2a**–**f** were prepared according to a modified procedure starting from known imidate hydrochlorides **1** and 1,1-disubstituted hydrazines (Scheme 1).[7] The microwave-assisted ring-closing reactions of the starting materials **2a**–**f** were conducted in microwave pressure-tubes at 100 W in DCM at moderate temperatures (Table 1). Previously unreported 5-cyanoimino-functionalized 1,2,4-triazolium ylides **5a**–**f** were synthesized in good yields of 64–92%

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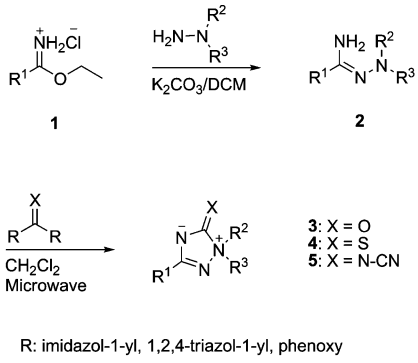
within only 2–3 min by treatment of compounds **2a**–**f** with 1.2 equiv. of diphenyl *N*-cyanimidocarbonate (Scheme 1).[8] Compounds **5a**–**f** are characterized by a strong C=N absorption band at 1641–1662 cm^{-1} and a sharp band of the cyano group at 2189–2195 cm^{-1}. The X-ray crystal structure of compound **5b** shows *E* configuration with regard to the C=N double bond (Figure 2).



Scheme 1. Synthesis of 1,2,4-triazolium ylides.

Table 1. Microwave synthesis of 1,2,4-triazolium ylides **3**–**5**.[a]

Entry	R^1	R^2	R^3	Compound (% yield)[b]
1	cyclohexyl	–$(CH_2)_2O(CH_2)_2$–		**3a** (82)
2	3,4-$(CH_3O)_2$-$C_6H_3CH_2$	CH_3	CH_3	**3b** (87)
3	3,4-Cl_2-$C_6H_3CH_2$	–$(CH_2)_5$–		**3c** (89)
4	4-Cl-$C_6H_4CH_2$	CH_3	CH_3	**3d** (84)
5	4-Cl-$C_6H_4CH_2$	–$(CH_2)_2NCH_3(CH_2)_2$–		**3e** (90)
6	2-thienylmethyl	–$(CH_2)_2O(CH_2)_2$–		**3f** (81)
7	cyclohexyl	–$(CH_2)_2O(CH_2)_2$–		**4a** (69)
8	3,4-$(CH_3O)_2$-$C_6H_3CH_2$	CH_3	CH_3	**4b** (86)
9	3,4-Cl_2-$C_6H_3CH_2$	–$(CH_2)_5$–		**4c** (77)
10	4-Cl-$C_6H_4CH_2$	CH_3	CH_3	**4d** (76)
11	4-Cl-$C_6H_4CH_2$	–$(CH_2)_2NCH_3(CH_2)_2$–		**4e** (78)
12	2-thienylmethyl	–$(CH_2)_2O(CH_2)_2$–		**4f** (74)
13	cyclohexyl	–$(CH_2)_2O(CH_2)_2$–		**5a** (92)
14	3,4-$(CH_3O)_2$-$C_6H_3CH_2$	CH_3	CH_3	**5b** (82)
15	3,4-Cl_2-$C_6H_3CH_2$	–$(CH_2)_5$–		**5c** (86)
16	4-Cl-$C_6H_4CH_2$	CH_3	CH_3	**5d** (75)
17	4-Cl-$C_6H_4CH_2$	–$(CH_2)_2NCH_3(CH_2)_2$–		**5e** (87)
18	2-thienylmethyl	–$(CH_2)_2O(CH_2)_2$–		**5f** (64)

[a] Microwave-assisted synthesis of compounds **3**–**5** was carried out by using a CEM Corporation Focused Microwave System, Model Discover. Parameters for the synthesis of compounds **3**–**5**: Discover mode; power: 100 W; ramp time: 1 min; hold time 2–3 min; temperature: 50 °C; pressure: 4 bar; PowerMax cooling. [b] Isolated yields.

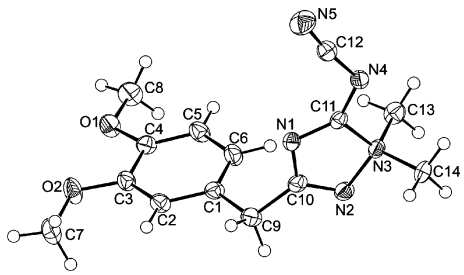


Figure 2. X-ray crystal structure of compound **5b**.

Next, amidrazones **2a**–**f** were treated with 1.2 equiv. of 1,1′-carbonylbis(1,2,4-triazole) and 1,1′-thiocarbonyldiimidazole, respectively to afford 1,2,4-triazolium ylides **3a**–**f** and **4a**–**f**, again within only 2–3 min and in high yields (Scheme 1, Table 1). Completion of the carbonylation reaction was monitored by IR spectroscopy and was accompanied by the appearance of a strong C=O absorption band at 1767–1774 cm^{-1}. In all cases a simple work up procedure followed by recrystallization from appropriate solvents furnished compounds **3**–**5** as analytically pure and solid products. The structures of all novel compounds were elucidated by ^1H and ^{13}C NMR, IR spectroscopy and elemental analysis (see the Exp. Sect.).

Conclusions

In conclusion, we have developed an efficient, fast and convenient method for the microwave-assisted preparation of various 5-functionalized 1,2,4-triazolium ylides. The synthesis of 5-cyanoimino-functionalized 1,2,4-triazolium ylides (**5**) has not been reported before. The first comprehensive method for the synthesis of 1,1-dialkyl-5-thioxo-1,2,4-triazolium ylides **4** has been described. Phosgene and thiophosgene have been successfully replaced by 1,1′-carbonylbis(1,2,4-triazole) and 1,1′-thiocarbonyldiimidazole in the synthesis of the 1,2,4-triazolium ylides **3** and **4**, respectively.

Experimental Section

General: Melting points: Electrothermal 9100 melting-point apparatus, uncorrected values. IR: ATI Genesis Series FT-IR spectrometer; KBr pellets unless otherwise stated. NMR: Bruker AMX 400 spectrometer (400 MHz for ^1H; 100 MHz for ^{13}C). NMR spectra were recorded in [D_6]DMSO solution with tetramethylsilane as the internal standard. Elemental analysis: Heraeus CHN-O-Rapid instrument. Microwave-assisted synthesis: CEM microwave model Discover. Thin-layer chromatography (TLC): Kieselgel 60 F_{254} (Macherey–Nagel) sheets; column chromatography: Kieselgel 60. Imidate hydrochlorides used for the synthesis of **2a**–**f** were prepared starting from the corresponding nitriles in accord with the standard Pinner synthesis.[7]

CCDC-662796 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of *N*′,*N*′-Disubstituted Carbohydrazonamides: Substrates **2a**–**f** were synthesized by a modified literature procedure.[7] The appropriate *N*′,*N*′-disubstituted hydrazine (18 mmol) was added dropwise to a suspension of the imidate hydrochloride salt (15 mmol) in dry dichloromethane (20 mL) and the reaction mixture was stirred at room temperature for 8 h. Afterwards, the solvent was evaporated and the remaining residue was quenched with an ice-cooled, saturated aqueous solution of potassium carbonate (15 mL). The mixture was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo. The remaining residues were crystallized from Et_2O/hexane to afford **2a**–**f** as solid compounds.

Recrystallization from EtOAc/hexane provided analytically pure products.

***N*′-(Morpholin-4-yl)cyclohexanecarboimidamide (2a):** Colourless solid; yield 60% (1.9 g), m.p. 116.3 °C. ^{1}H NMR: δ = 1.11–1.96 (m, 11 H, cyclohexyl, C_6H_{11}), 2.43 (s, 4 H, 3,5-H), 3.63 (s, 4 H, 2,6-H), 5.72 (s, 2 H, NH_2) ppm. ^{13}C NMR: δ = 25.96 (cyclohexyl, C-1), 26.14 (cyclohexyl, C-2,6), 30.46 (cyclohexyl, C-3,5), 42.27 (cyclohexyl, C-4), 54.87 (C-3,5), 66.21 (C-2,6), 163.04 (C=N) ppm. IR: $\tilde{\nu}$ = 3408 (NH_2), 1610 (C=N) cm^{-1}. $C_{11}H_{21}N_3O$ (211.31): calcd. C 62.53, H 10.02, N 19.89; found C 62.39, H 9.98, N 19.53.

(1*Z*)-2-(3,4-Dimethoxyphenyl)-*N*′,*N*′-dimethylethanehydrazonamide (2b): Colourless solid; yield 65% (2.3 g), m.p. 68.1 °C. ^{1}H NMR: δ = 2.26 [s, 6 H, N(CH_3)$_2$], 3.16 (s, 2 H, 2-H), 3.71 [d, $^3J_{H,H}$ = 2.54 Hz, 6 H, 3,4-(CH_3O)$_2$-Ph], 5.76 (s, 2 H, NH_2), 6.77–6.86 (m, 2 H, 5′,6′-H), 6.92 (d, $^3J_{H,H}$ = 1.78 Hz, 1 H, 2′-H) ppm. ^{13}C NMR: δ = 39.06 (C-2), 46.84 [N(*C*H$_3$)$_2$], 55.64, 55.88 [3,4-(CH_3O)$_2$-Ph], 112.07, 112.61, 120.73 (C-2′, C-5′, C-6′), 130.89, 147.66, 148.78 (C-1′, C-3′, C-4′), 158.25 (C-1) ppm. IR: $\tilde{\nu}$ = 3318 (NH_2), 1639 (C=N) cm^{-1}. $C_{12}H_{19}N_3O_2$ (237.30): calcd. C 60.74, H 8.07, N 17.71; found C 60.69, H 8.15, N 17.33.

(1*Z*)-2-(3,4-Dichlorophenyl)-*N*′-(piperidin-1-yl)ethanimidamide (2c): Colourless solid; yield 61% (2.6 g), m.p. 126.0 °C. ^{1}H NMR: δ = 1.35 (s, 2 H, piperidine, 4-H), 1.53–1.59 (m, 4 H, piperidine, 3,5-H), 2.44 (s, 4 H, piperidine 2,6-H), 3.29 (s, 2 H, 2-H), 6.03 (br. s, 2 H, NH_2), 7.27–7.29 (m, 1 H, 6′-H), 7.54–7.56 (m, 2 H, 2′,5′-H) ppm. ^{13}C NMR: δ = 24.02 (piperidine, C-4), 25.51 (piperidine, C-3,5), 38.20 (C-2), 55.51 (piperidine, C-2,6), 129.21, 130.61, 130.82 (C-6′, C-5′, C-2′), 130.94, 134.68 (C-3′, C-4′, C-1′), 157.51 (C-1) ppm. IR: $\tilde{\nu}$ = 3379 (NH_2), 1628 (C=N) cm^{-1}. $C_{13}H_{17}Cl_2N_3$ (286.21): calcd. C 54.56, H 5.99, N 14.68; found C 54.24, H 6.05, N 14.62.

(1*Z*)-2-(4-Chlorophenyl)-*N*′,*N*′-dimethylethanehydrazonamide (2d): Colourless solid; yield 62% (2.0 g), m.p. 136.0 °C. ^{1}H NMR: δ = 2.25 [s, 6 H, N(CH_3)$_2$], 3.23 (s, 2 H, 2-H), 5.86 (s, 2 H, NH_2), 7.29–7.35 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 38.78 (C-2), 46.81 [N(*C*H$_3$)$_2$], 128.39, 130.63 (C-3′,5′, C-2′,6′), 131.18, 137.64 (C-4′, C-1′), 157.65 (C-1) ppm. IR: $\tilde{\nu}$ = 3287 (NH_2), 1653 (C=N) cm^{-1}. $C_{10}H_{14}ClN_3$ (211.70): calcd. C 56.74, H 6.67, N 19.85; found C 56.64, H 6.70, N 19.73.

(1*Z*)-2-(4-Chlorophenyl)-*N*′-(4-methylpiperazin-1-yl)ethanimidamide (2e): Colourless solid; yield 62% (2.5 g), m.p. 146.5 °C. ^{1}H NMR: δ = 2.14 (s, 4 H, 4-Me-piperazine, 3,5-H), 2.40 (br. s, 4 H, 4-Me-piperazine, 2,6-H), 3.25 (s, 2 H, 2-H), 3.37 (s, 3 H, NCH_3), 5.87 (s, 2 H, NH_2), 7.29–7.35 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 38.75 (C-2), 46.01 (N*C*H$_3$), 53.97 (4-Me-piperazine, C-3,5), 54.68 (4-Me-piperazine, C-2,6), 128.40, 130.62 (C-3′,5′, C-2′,6′), 131.20, 137.59 (C-4′, C-1′), 158.04 (C-1) ppm. IR: $\tilde{\nu}$ = 3375 (NH_2), 1634 (C=N) cm^{-1}. $C_{13}H_{19}ClN_4$ (266.78): calcd. C 58.53, H 7.18, N 21.00; found C 58.24, H 7.27, N 20.79.

(1*Z*)-*N*′-Morpholin-4-yl-2-(2-thienyl)ethanimidamide (2f): Pale-yellow solid; yield 56% (1.9 g), m.p. 87.0 °C. ^{1}H NMR: δ = 2.50 (s, 4 H, morpholine, 3,5-H), 3.46 (s, 2 H, 2-H), 3.65 (s, 4 H, morpholine, 2,6-H), 5.97 (s, 2 H, NH_2), 6.92 (d, $^3J_{H,H}$ = 3.56 Hz, 2 H, 3′,4′-H), 7.31 (t, $^3J_{H,H}$ = 3.30 Hz, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 34.17 (C-2), 54.75 (morpholine, C-3,5), 66.14 (morpholine, C-2,6), 124.76, 125.94, 126.92 (C-5′, C-4′, C-3′), 140.83 (C-2′), 157.89 (C-1) ppm. IR: $\tilde{\nu}$ = 3421 (NH_2), 1622 (C=N) cm^{-1}. $C_{10}H_{15}N_3OS$ (225.31): calcd. C 53.31, H 6.71, N 18.65; found C 53.45, H 6.73, N 18.34.

Microwave-Assisted Synthesis of Compounds 3a–f. General Procedure: Compounds **2a**–**f** (2 mmol) dissolved in dry dichloromethane (5 mL) and 1,1′-carbonylbis(1,2,4-triazole) (394 mg, 2.4 mmol) were added to a 10-mL microwave glass pressure-tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for 2–3 min. The reaction mixture was cooled to room temperature and transferred to a round-bottomed flask. The solvent was evaporated, ethyl acetate (20 mL) was added and the mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate (3 × 5 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated. The remaining residue was crystallized from Et_2O/hexane. Recrystallization from THF/hexane provided compounds **3a**–**f** as analytically pure solids. Microwave parameters for compounds **3a**–**f**: Discover mode; power: 100 W; ramp time: 1 min; hold time: 2–3 min; temperature: 50 °C; pressure: 4 bar; PowerMax cooling mode.

2-Cyclohexyl-4-oxo-8-oxa-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (3a): Colourless solid; yield 82% (389 mg), m.p. 115.0 °C. ^{1}H NMR: δ = 1.18–1.83 (m, 10 H, cyclohexyl, C_5H_{10}), 2.32–2.39 (m, 1 H, cyclohexyl, CH), 2.80–2.83 (d, $^3J_{H,H}$ = 12.46 Hz, 2 H, morpholine, 3-H), 3.36–3.43 (m, 2 H, morpholine, 5-H), 3.93–4.04 (m, 4 H, morpholine, 2,6-H) ppm. ^{13}C NMR: δ = 25.34 (cyclohexyl, C-3,5), 25.85 (cyclohexyl, C-4), 29.56 (cyclohexyl, C-2,6), 39.22 (cyclohexyl, C-1), 55.66 (C-7,9), 62.37 (C-6,10), 170.39 (C-2), 187.29 (C-4) ppm. IR: $\tilde{\nu}$ = 1773 (C=O) cm^{-1}. $C_{12}H_{19}N_3O_2$ (237.30): calcd. C 60.74, H 8.07, N 17.71; found C 60.56, H 8.30, N 17.63. Hold time: 2.5 min.

3-(3,4-Dimethoxybenzyl)-1,1-dimethyl-5-oxo-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (3b): Colourless solid; yield 87% (458 mg), m.p. 87.4 °C. ^{1}H NMR: δ = 2.96 [s, 6 H, N(CH_3)$_2$], 3.56 [s, 2 H, 3,4-(CH_3O)$_2$-PhCH_2], 3.72 [d, $^3J_{H,H}$ = 1.79 Hz, 6 H, 3,4-(CH_3O)$_2$-Ph], 6.78–6.80 (m, 1 H, 2′-H), 6.86–6.88 (m, 2 H, 5′,6′-H) ppm. ^{13}C NMR: δ = 35.58 [3,4-(CH_3O)$_2$-Ph*C*H$_2$], 47.66 [N(*C*H$_3$)$_2$], 55.41, 55.52 [3,4-(CH_3O)$_2$-Ph], 111.86, 112.90, 121.02 (C-5′, C-2′, C-6′), 127.85, 147.65, 148.55 (C-1′, C-4′, C-3′), 170.01 (C-3), 181.88 (C-5) ppm. IR: $\tilde{\nu}$ = 1773 (C=O) cm^{-1}. $C_{13}H_{17}N_3O_3$ (263.30): calcd. C 59.30, H 6.51, N 15.96; found C 59.12, H 6.62, N 15.65. Hold time: 2 min.

2-(3,4-Dichlorobenzyl)-4-oxo-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (3c): Colourless solid; yield 89% (556 mg), m.p. 116.0 °C. ^{1}H NMR: δ = 1.51–2.00 (m, 6 H, 7,8,9-H), 2.86–2.89 (m, 2 H, 6-H), 3.23–3.30 (m, 2 H, 10-H), 3.73 (s, 2 H, 3,4-Cl_2-PhCH_2), 7.30–7.33 (m, 1 H, 2′-H), 7.56–7.61 (m, 2 H, 5′,6′-H) ppm. ^{13}C NMR: δ = 20.76 (C-8), 21.02 (C-7,9), 35.00 (3,4-Cl_2-Ph*C*H$_2$), 56.61 (C-6,10), 129.34 (C-4′), 129.52, 130.35 (C-6′, C-5′), 130.71 (C-3′), 131.14 (C-2′), 136.88 (C-1′), 171.04 (C-2), 181.48 (C-4) ppm. IR: $\tilde{\nu}$ = 1774 (C=O) cm^{-1}. $C_{14}H_{15}Cl_2N_3O$ (312.20): calcd. C 53.86, H 4.84, N 13.46; found C 53.87, H 4.90, N 13.26. Hold time: 2 min.

3-(4-Chlorobenzyl)-1,1-dimethyl-5-oxo-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (3d): Colourless solid; yield 84% (524 mg), m.p. 131.5 °C. ^{1}H NMR: δ = 2.96 [s, 6 H, N(CH_3)$_2$], 3.66 (s, 2 H, 4-Cl-PhCH_2), 7.31–7.38 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 35.70 (4-Cl-Ph*C*H$_2$), 48.08 [N(*C*H$_3$)$_2$], 128.61 (C-3′, C-5′), 131.41 (C-2′, C-6′), 131.74, 134.95 (C-1′, C-4′), 170.38 (C-3), 181.83 (C-5) ppm. IR: $\tilde{\nu}$ = 1771 (C=O) cm^{-1}. $C_{11}H_{12}ClN_3O$ (237.69): calcd. C 55.59, H 5.09, N 17.68; found C 55.41, H 5.45, N 17.31. Hold time: 2 min.

2-(4-Chlorobenzyl)-8-methyl-4-oxo-1,3,5,8-tetraazaspiro[4.5]dec-1-en-5-ium-3-ide (3e): Colourless solid; yield 90% (527 mg), m.p. 196.2 °C. ^{1}H NMR: δ = 2.29 (s, 3 H, NCH_3), 2.54–2.61 (m, 2 H, 6-H), 2.88–2.91 (m, 4 H, 7,9-H), 3.30–3.39 (m, 2 H, 10-H), 3.69 (s, 2 H, 4-Cl-PhCH_2), 7.32–7.38 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 35.43 (N*C*H$_3$), 45.14 (4-Cl-Ph*C*H$_2$), 49.57 (C-7,9), 55.83 (C-6,10), 128.23 (C-3′,5′), 130.88 (C-2′,6′), 131.35 (C-1′), 134.65 (C-4′),

170.23 (C-2), 182.02 (C-4) ppm. IR: $\tilde{\nu}$ = 1774 (C=O) cm^{-1}. $C_{14}H_{17}ClN_4O$ (292.77): calcd. C 57.44, H 5.85, N 19.14; found C 57.25, H 6.18, N 18.82. Hold time: 2.5 min.

4-Oxo-2-(2-thienylmethyl)-8-oxa-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (3f): Pale-brown solid; yield 81% (407 mg), m.p. 111.0 °C. ^1H NMR: δ = 2.87–2.90 (m, 2 H, 6-H), 3.40–3.47 (m, 2 H, 10-H), 3.94 (s, 2 H, 2-thienyl-CH_2), 3.98–4.06 (m, 4 H, 7,9-H), 6.95–7.01 (m, 2 H, 3′,4′-H), 7.39–7.40 (m, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 30.80 (2-thienyl-CH_2), 55.24 (C-7,9), 61.97 (C-6,10), 125.21, 126.64, 126.75 (C-5′, C-4′, C-3′), 136.85 (C-1′), 169.75 (C-2), 181.95 (C-4) ppm. IR: $\tilde{\nu}$ = 1767 (C=O) cm^{-1}. $C_{11}H_{13}N_3O_2S$ (251.31): calcd. C 52.57, H 5.21, N 16.72; found C 52.38, H 5.31, N 16.57. Hold time: 3 min.

Microwave-Assisted Synthesis of Compounds 4a–f. General Procedure: Compounds **2a**–**f** (2 mmol) dissolved in dry dichloromethane (5 mL) and 1,1′-thiocarbonyldiimidazole (428 mg, 2.4 mmol) were added to a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for 2–3 min. The reaction mixture was cooled to room temperature and transferred to a round-bottomed flask. The solvent was evaporated, ethyl acetate (20 mL) was added and the mixture was washed with 1 M hydrochloric acid (3 × 5 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated. The remaining residues were purified by filtration through a short silica gel column (3 cm) with EtOAc/hexane (1:1) as eluent. Crystallization from EtOAc/hexane provided **4a**–**f** as analytically pure solids. Microwave parameters for compounds **4a**–**f**: Discover mode; power: 100 W; ramp time: 1 min; hold time: 2–3 min; temperature: 50 °C; pressure: 4 bar; PowerMax cooling mode.

2-Cyclohexyl-4-thioxo-8-oxa-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (4a): Colourless solid; yield 69% (350 mg), m.p. 120.9 °C. ^1H NMR: δ = 1.17–1.91 (m, 10 H, cyclohexyl, C_5H_{10}), 2.53–2.60 (m, 1 H, cyclohexyl, CH), 2.80 (br. s, 2 H, 6-H), 3.71 (br. s, 2 H, 10-H), 4.06 (s, 4 H, 7,9-H) ppm. ^{13}C NMR: δ = 24.81 (cyclohexyl, C-3,5), 25.37 (cyclohexyl, C-4), 29.08 (C-2,6), 59.13 (C-7,9), 62.48 (C-6,10), 184.74 (C-2), 197.96 (C-4) ppm. IR: $\tilde{\nu}$ = 2928, 2854, 1544 cm^{-1}. $C_{12}H_{19}N_3OS$ (253.37): calcd. C 56.89, H 7.56, N 16.58; found C 56.84, H 7.69, N 16.51. Hold time: 3 min.

3-(3,4-Dimethoxybenzyl)-1,1-dimethyl-5-thioxo-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (4b): Colourless solid; yield 86% (480 mg), m.p. 136.0 °C. ^1H NMR: δ = 3.10 [s, 6 H, N(CH_3)$_2$], 3.73 [d, J = 2.03 Hz, 6 H, 3,4-(CH_3O)$_2$-Ph], 3.76 [s, 2 H, 3,4-(CH_3O)$_2$-PhCH_2], 6.80–6.83 (m, 1 H, 6′-H), 6.88–6.90 (m, 2 H, 5′,2′-H) ppm. ^{13}C NMR: δ = 34.56 [3,4-(CH_3O)$_2$-PhCH_2], 51.68 [N(CH_3)$_2$], 55.89 [3,4-(CH_3O)$_2$-Ph], 112.26, 113.39, 121.61 (C-5′, C-2′, C-6′), 127.52 (C-1′), 148.18, 149.00 (C-4′, C-3′), 180.32 (C-3), 198.45 (C-5) ppm. IR: $\tilde{\nu}$ = 1517, 1478, 1261 cm^{-1}. $C_{13}H_{17}N_3O_2S$ (279.36): calcd. C 55.89, H 6.13, N 15.04; found C 55.55, H 6.14, N 14.92. Hold time: 2.5 min.

2-(3,4-Dichlorobenzyl)-4-thioxo-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (4c): Pale-yellow solid; yield 77% (505 mg), m.p. 139.0 °C. ^1H NMR: δ = 1.52–2.06 (m, 6 H, 7,8,9-H), 2.82 (d, J = 11.80 Hz, 2 H, 6-H), 3.56 (t, J = 12.80 Hz, 2 H, 10-H), 3.93 (s, 2 H, 3,4-Cl_2-PhCH_2), 7.32–7.35 (m, 1 H, 6′-H), 7.59 (d, J = 8.29 Hz, 1 H, 2′-H), 7.64 (d, J = 2.01 Hz, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 20.71 (C-8), 21.70 (C-7,9), 33.67 (3,4-Cl_2-PhCH_2), 61.00 (C-6,10), 129.60 (C-4′), 129.71, 130.46 (C-6′, C-5′), 130.82 (C-3′), 131.33 (C-2′), 136.25 (C-1′), 179.48 (C-2), 194.60 (C-4) ppm. IR: $\tilde{\nu}$ = 2953, 1557, 1442, 1334 cm^{-1}. $C_{14}H_{15}Cl_2N_3S$ (328.27): calcd. C 51.23, H 4.61, N 12.80; found C 51.11, H 4.79, N 12.66. Hold time: 2.5 min.

3-(4-Chlorobenzyl)-1,1-dimethyl-5-thioxo-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (4d): Pale-yellow solid; yield 76% (386 mg), m.p. 138.9 °C. ^1H NMR: δ = 3.10 [s, 6 H, N(CH_3)$_2$], 3.86 (s, 2 H, 4-Cl-PhCH_2), 7.33–7.40 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 33.90 (4-Cl-PhCH_2), 51.32 [N(CH_3)$_2$], 128.33, 131.16 (C-3′,5′, C-2′,6′), 131.59, 133.96 (C-1′, C-4′), 179.54 (C-3), 198.17 (C-5) ppm. IR: $\tilde{\nu}$ = 2953, 1557, 1442, 1334 cm^{-1}. $C_{11}H_{12}ClN_3S$ (253.76): calcd. C 52.07, H 4.77, N 16.56; found C 51.83, H 4.84, N 16.41. Hold time: 3 min.

2-(4-Chlorobenzyl)-8-methyl-4-thioxo-1,3,5,8-tetraazaspiro[4.5]dec-1-en-5-ium-3-ide (4e): Colourless solid; yield 78% (482 mg), m.p. 209.5 °C. ^1H NMR: δ = 2.32 (s, 3 H, NCH_3), 2.66 (s, 2 H, 6-H), 2.84–2.97 (m, 4 H, 7,9-H), 3.70 (s, 2 H, 10-H), 3.89 (s, 2 H, 4-Cl-PhCH_2), 7.34–7.40 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 34.44 (4-Cl-PhCH_2), 45.41 (NCH_3), 50.50 (C-7,9), 60.19 (C-6,10), 128.76, 131.49 (C-3′,5′, C-2′,6′), 131.98, 134.43 (C-1′, C-4′), 180.41 (C-2), 199.04 (C-4) ppm. IR: $\tilde{\nu}$ = 1560, 1458, 1340 cm^{-1}. $C_{14}H_{17}ClN_4S$ (308.84): calcd. C 54.45, H 5.55, N 18.14; found C 54.13, H 5.65, N 17.97. Hold time: 2.5 min.

2-(2-Thienylmethyl)-4-thioxo-8-oxa-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (4f): Orange-brown solid; yield 74% (396 mg), m.p. 136.0 °C. ^1H NMR: δ = 2.86 (br. s, 2 H, 6-H), 3.72 (br. s, 2 H, 10-H), 4.07 (s, 4 H, 7,9-H), 4.14 (s, 2 H, 2-thienyl-CH_2), 6.98–7.00 (m, 1 H, 3′-H), 7.03–7.04 (m, 1 H, 4′-H), 7.42–7.44 (m, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 29.42 (2-thienyl-CH_2), 59.15 (C-7,9), 62.46 (C-6,10), 125.50, 126.91, 127.05 (C-5′, C-4′, C-3′), 136.10 (C-2′), 179.97 (C-2), 198.25 (C-4) ppm. IR: $\tilde{\nu}$ = 1555, 1456, 1331 cm^{-1}. $C_{11}H_{13}N_3OS_2$ (267.37): calcd. C 49.41, H 4.90, N 15.72; found C 49.06, H 5.01, N 15.47. Hold time: 3 min.

Microwave-Assisted Synthesis of Compounds 5a–f. General Procedure: Compounds **2a**–**f** (2 mmol) dissolved in dry dichloromethane (5 mL) and diphenyl *N*-cyanimidocarbonate (572 mg, 2.4 mmol) were added to a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for 2–3 min. The reaction mixture was cooled to room temperature and was transferred to a round-bottomed flask. The solvent was evaporated, ethyl acetate (20 mL) was added and the mixture was washed with a saturated aqueous solution of potassium carbonate (3 × 5 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated. The remaining residues were purified by column chromatography with EtOAc/hexane (1:1) as eluent. Crystallization from THF/hexane provided **5a**–**f** as analytically pure solids. Microwave parameters for compounds **5a**–**f**: Discover mode; power: 100 W; ramp time: 1 min; hold time: 2–3 min; temperature: 50 °C; pressure: 4 bar; PowerMax cooling mode.

(4*E*)-4-(Cyanoimino)-2-cyclohexyl-8-oxa-1,3,5-triazaspiro[4.5]dec-1-en-5-ium-3-ide (5a): Colourless solid; yield 92% (481 mg), m.p. 139.5 °C. ^1H NMR: δ = 1.17–1.90 (m, 10 H, cyclohexyl, C_5H_{10}), 2.47–2.55 (m, 1 H, cyclohexyl, CH), 3.21–3.24 (d, $^3J_{H,H}$ = 12.72 Hz, 2 H, 6-H), 3.55–3.62 (m, 2 H, 10-H), 3.48–4.09 (m, 4 H, 7,9-H) ppm. ^{13}C NMR: δ = 25.16 (cyclohexyl, C-3,5), 25.70 (cyclohexyl, C-4), 29.40 (cyclohexyl, C-2,6), 38.17 (cyclohexyl, C-1), 59.94 (C-7,9), 62.39 (C-6,10), 115.23 [N(*C*N)], 178.52 (C-2), 184.13 (C-4) ppm. IR: $\tilde{\nu}$ = 2193 (CN), 1650 (C=N) cm^{-1}. $C_{13}H_{19}N_5O$ (261.33): calcd. C 59.75, H 7.33, N 26.80; found C 59.73, H 7.36, N 26.80. Hold time: 3 min.

(5*E*)-5-(Cyanoimino)-3-(3,4-dimethoxybenzyl)-1,1-dimethyl-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (5b): Colourless solid; yield 82% (471 mg), m.p. 165.4 °C. ^1H NMR: δ = 3.24 [s, 6 H, N(CH_3)$_2$], 3.72 [s, 2 H, 3,4-(CH_3O)$_2$-PhCH_2], 3.73 [d, $^3J_{H,H}$ = 2.26 Hz, 6 H, 3,4-(CH_3O)$_2$-Ph], 6.81–6.84 (m, 1 H, 6′-H), 6.89–6.91 (m, 2 H, 2′,5′-H) ppm. ^{13}C NMR: δ = 34.20 [3,4-(CH_3O)$_2$-PhCH_2], 51.32

[N(*C*H$_3$)$_2$], 55.41, 55.50 [3,4-(C*H*$_3$O)$_2$-Ph], 111.91, 113.02 (C-5′, C-2′), 114.73 [N(*C*N)], 121.23 (C-6′), 126.81 (C-1′), 147.86, 148.63 (C-4′, C-3′), 178.40 (C-3), 179.01 (C-5) ppm. IR: $\tilde{\nu}$ = 2195 (CN), 1655 (C=N) cm^{-1}. $C_{14}H_{17}N_5O_2$ (287.32): calcd. C 58.52, H 5.96, N 24.37; found C 58.52, H 6.13, N 24.25. Hold time: 2.5 min.

(4*E*)-4-(Cyanoimino)-2-(3,4-dichlorobenzyl)-1,3,5-triazaspiro[4.5]-dec-1-en-5-ium-3-ide (5c): Colourless solid; yield 86% (578 mg), m.p. 194.5 °C. ^{1}H NMR: δ = 1.54–2.04 (m, 6 H, 7,8,9-H), 3.23–3.26 (d, $^3J_{H,H}$ = 11.70 Hz, 2 H, 6-H), 3.43–3.50 (m, 2 H, 10-H), 3.89 (s, 2 H, 3,4-Cl$_2$-PhC*H*$_2$), 7.33–7.36 (m, 1 H, 6′-H), 7.60 (d, $^3J_{H,H}$ = 8.14 Hz, 1 H, 2′-H), 7.65 (d, $^3J_{H,H}$ = 2.04 Hz, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 20.58 (C-8), 21.64 (C-7,9), 34.20 (3,4-Cl$_2$-Ph*C*H$_2$), 61.64 (C-6,10), 115.18 [N(*C*N)], 130.09, 130.90 (C-6′, C-5′), 131.26 (C-3′,4′), 131.73 (C-2′), 136.35 (C-1′), 178.88 (C-2), 179.82 (C-4) ppm. IR: $\tilde{\nu}$ = 2190 (CN), 1642 (C=N) cm^{-1}. $C_{15}H_{15}Cl_2N_5$ (336.23): calcd. C 53.59, H 4.50, N 20.83; found C 53.57, H 4.61, N 20.81. Hold time: 2.5 min.

(5*E*)-3-(4-Chlorobenzyl)-5-(cyanoimino)-1,1-dimethyl-1,5-dihydro-1,2,4-triazol-1-ium-4-ide (5d): Colourless solid; yield 75% (392 mg), m.p. 156.3 °C. ^{1}H NMR: δ = 3.24 [s, 6 H, N(C*H*$_3$)$_2$], 3.83 (s, 2 H, 4-Cl-PhC*H*$_2$), 7.34–7.41 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 34.47 (4-Cl-Ph*C*H$_2$), 51.74 [N(*C*H$_3$)$_2$], 115.08 [N(*C*N)], 128.76 (C-3′,5′), 131.59 (C-2′,6′), 132.06 (C-1′), 134.05 (C-4′), 178.82 (C-3), 179.01 (C-5) ppm. IR: $\tilde{\nu}$ = 2195 (CN), 1662 (C=N) cm^{-1}. $C_{12}H_{12}ClN_5$ (261.72): calcd. C 55.07, H 4.62, N 26.76; found 55.27, H 4.78, N 26.84. Hold time: 2.5 min.

(4*E*)-2-(4-Chlorobenzyl)-4-(cyanoimino)-8-methyl-1,3,5,8-tetraazaspiro[4.5]dec-1-en-5-ium-3-ide (5e): Colourless solid; yield 87% (551 mg), m.p. 250 °C (dec.). ^{1}H NMR: δ = 2.31 (s, 3 H, NC*H*$_3$), 2.62–2.68 (m, 2 H, 7-H), 2.96 (d, $^3J_{H,H}$ = 12.46 Hz, 2 H, 9-H), 3.28 (d, $^3J_{H,H}$ = 12.21 Hz, 2 H, 6-H), 3.51–3.58 (m, 2 H, 10-H), 3.85 (s, 2 H, 4-Cl-PhC*H*$_2$), 7.35–7.41 (m, 4 H, 4-Cl-Ph) ppm. ^{13}C NMR: δ = 34.18 (4-Cl-Ph*C*H$_2$), 44.91 (N*C*H$_3$), 49.54 (C-7,9), 60.31 (C-6,10), 114.68 [N(*C*N)], 128.39, 131.05 (C-3′,5′, C-2′,6′), 131.67, 133.72 (C-1′, C-4′), 178.67 (C-2), 178.99 (C-4) ppm. IR: $\tilde{\nu}$ = 2189 (CN), 1655 (C=N) cm^{-1}. $C_{15}H_{17}ClN_6$ (316.80): calcd. C 56.87, H 5.41, N 26.53; found 56.74, H 5.53, N 26.42. Hold time: 2.5 min.

(4*E*)-4-(Cyanoimino)-2-(2-thienylmethyl)-8-oxa-1,3,5-triazaspiro[4.5]-dec-1-en-5-ium-3-ide (5f): Pale-rose solid; yield 64% (352 mg), m.p. 174.2 °C. ^{1}H NMR: δ = 3.27 (d, $^3J_{H,H}$ = 12.80 Hz, 2 H, 6-H), 3.58–3.65 (m, 2 H, 10-H), 3.99–4.11 (m, 4 H, 7,9-H), 4.10 (s, 2 H, 2-thienyl-C*H*$_2$), 6.98–7.00 (m, 1 H, 3′-H), 7.05–7.06 (m, 1 H, 4′-H), 7.43–7.45 (m, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 29.54 (2-thienyl-*C*H$_2$), 59.63 (C-7,9), 61.98 (C-6,10), 114.45 [N(*C*N)], 125.56, 126.92, 127.16 (C-5′, C-4′, C-3′), 135.72 (C-2′), 178.21 (C-2), 178.93 (C-4) ppm. IR: $\tilde{\nu}$ = 2189 (CN), 1641 (C=N) cm^{-1}. $C_{12}H_{13}N_5OS$ (275.33): calcd. C 52.35, H 4.76, N 25.44; found C 52.12, H 4.93, N 25.19. Hold time: 2.5 min.

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