

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

Mehdi Khankischpur^[a] and Thomas Kurz^{*[b]}

Keywords: Ylides / Nitrogen heterocycles / Cyclization / Microwave-assisted synthesis

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.

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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-cyanoimino-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.

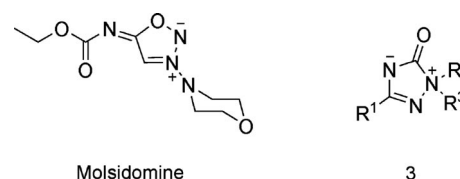


Figure 1. Heterocyclic betaines Molsidomine and **3**.

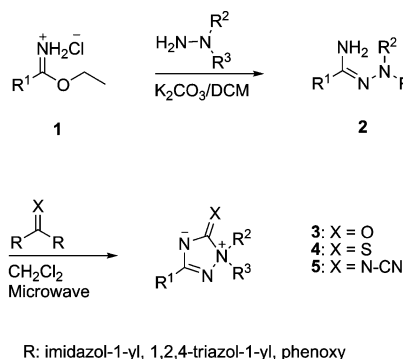
Results and Discussion

Substrates **2a–f** were prepared according to a modified procedure starting from known imide 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%

[a] Institute of Pharmacy, University of Hamburg, Bundesstr. 45, 20146 Hamburg
E-mail: khanki@chemie.uni-hamburg.de

[b] Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, 40255 Düsseldorf, Germany
E-mail: Thomas.Kurz@uni-duesseldorf.de

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) ₂ O(CH ₂) ₂ –		3a (82)
2	3,4-(CH ₃ O) ₂ -C ₆ H ₃ CH ₂	CH ₃	CH ₃	3b (87)
3	3,4-Cl ₂ -C ₆ H ₃ CH ₂	–(CH ₂) ₅ –		3c (89)
4	4-Cl-C ₆ H ₄ CH ₂	CH ₃	CH ₃	3d (84)
5	4-Cl-C ₆ H ₄ CH ₂	–(CH ₂) ₂ NCH ₃ (CH ₂) ₂ –		3e (90)
6	2-thienylmethyl	–(CH ₂) ₂ O(CH ₂) ₂ –		3f (81)
7	cyclohexyl	–(CH ₂) ₂ O(CH ₂) ₂ –		4a (69)
8	3,4-(CH ₃ O) ₂ -C ₆ H ₃ CH ₂	CH ₃	CH ₃	4b (86)
9	3,4-Cl ₂ -C ₆ H ₃ CH ₂	–(CH ₂) ₅ –		4c (77)
10	4-Cl-C ₆ H ₄ CH ₂	CH ₃	CH ₃	4d (76)
11	4-Cl-C ₆ H ₄ CH ₂	–(CH ₂) ₂ NCH ₃ (CH ₂) ₂ –		4e (78)
12	2-thienylmethyl	–(CH ₂) ₂ O(CH ₂) ₂ –		4f (74)
13	cyclohexyl	–(CH ₂) ₂ O(CH ₂) ₂ –		5a (92)
14	3,4-(CH ₃ O) ₂ -C ₆ H ₃ CH ₂	CH ₃	CH ₃	5b (82)
15	3,4-Cl ₂ -C ₆ H ₃ CH ₂	–(CH ₂) ₅ –		5c (86)
16	4-Cl-C ₆ H ₄ CH ₂	CH ₃	CH ₃	5d (75)
17	4-Cl-C ₆ H ₄ CH ₂	–(CH ₂) ₂ NCH ₃ (CH ₂) ₂ –		5e (87)
18	2-thienylmethyl	–(CH ₂) ₂ O(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.

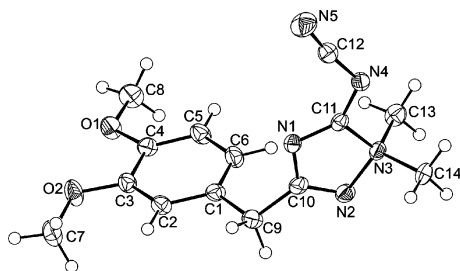


Figure 2. X-ray crystal structure of compound **5b**.

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 ¹³C 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 ¹³C). NMR spectra were recorded in [D₆]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 F₂₅₄ (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 Na₂SO₄, filtered and concentrated in vacuo. The remaining residues were crystallized from Et₂O/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. ¹H NMR: δ = 1.11–1.96 (m, 11 H, cyclohexyl, C₆H₁₁), 2.43 (s, 4 H, 3,5-H), 3.63 (s, 4 H, 2,6-H), 5.72 (s, 2 H, NH₂) ppm. ¹³C 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: ν̄ = 3408 (NH₂), 1610 (C=N) cm⁻¹. C₁₁H₂₁N₃O (211.31): calcd. C 62.53, H 10.02, N 19.89; found C 62.39, H 9.98, N 19.53.

(1Z)-2-(3,4-Dimethoxyphenyl)-*N'*,*N'*-dimethylethanehydrazonamide (2b): Colourless solid; yield 65% (2.3 g), m.p. 68.1 °C. ¹H NMR: δ = 2.26 [s, 6 H, N(CH₃)₂], 3.16 (s, 2 H, 2-H), 3.71 [d, ³J_{H,H} = 2.54 Hz, 6 H, 3,4-(CH₃O)₂-Ph], 5.76 (s, 2 H, NH₂), 6.77–6.86 (m, 2 H, 5',6'-H), 6.92 (d, ³J_{H,H} = 1.78 Hz, 1 H, 2'-H) ppm. ¹³C NMR: δ = 39.06 (C-2), 46.84 [N(CH₃)₂], 55.64, 55.88 [3,4-(CH₃O)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: ν̄ = 3318 (NH₂), 1639 (C=N) cm⁻¹. C₁₂H₁₉N₃O₂ (237.30): calcd. C 60.74, H 8.07, N 17.71; found C 60.69, H 8.15, N 17.33.

(1Z)-2-(3,4-Dichlorophenyl)-*N'*-(piperidin-1-yl)ethanimidamide (2c): Colourless solid; yield 61% (2.6 g), m.p. 126.0 °C. ¹H 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, NH₂), 7.27–7.29 (m, 1 H, 6'-H), 7.54–7.56 (m, 2 H, 2',5'-H) ppm. ¹³C 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: ν̄ = 3379 (NH₂), 1628 (C=N) cm⁻¹. C₁₃H₁₇Cl₂N₃ (286.21): calcd. C 54.56, H 5.99, N 14.68; found C 54.24, H 6.05, N 14.62.

(1Z)-2-(4-Chlorophenyl)-*N'*,*N'*-dimethylethanehydrazonamide (2d): Colourless solid; yield 62% (2.0 g), m.p. 136.0 °C. ¹H NMR: δ = 2.25 [s, 6 H, N(CH₃)₂], 3.23 (s, 2 H, 2-H), 5.86 (s, 2 H, NH₂), 7.29–7.35 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 38.78 (C-2), 46.81 [N(CH₃)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: ν̄ = 3287 (NH₂), 1653 (C=N) cm⁻¹. C₁₀H₁₄ClN₃ (211.70): calcd. C 56.74, H 6.67, N 19.85; found C 56.64, H 6.70, N 19.73.

(1Z)-2-(4-Chlorophenyl)-*N'*-(4-methylpiperazin-1-yl)ethanimidamide (2e): Colourless solid; yield 62% (2.5 g), m.p. 146.5 °C. ¹H 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, NCH₃), 5.87 (s, 2 H, NH₂), 7.29–7.35 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 38.75 (C-2), 46.01 (NCH₃), 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: ν̄ = 3375 (NH₂), 1634 (C=N) cm⁻¹. C₁₃H₁₉ClN₄ (266.78): calcd. C 58.53, H 7.18, N 21.00; found C 58.24, H 7.27, N 20.79.

(1Z)-*N'*-Morpholin-4-yl-2-(2-thienyl)ethanimidamide (2f): Pale-yellow solid; yield 56% (1.9 g), m.p. 87.0 °C. ¹H 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, NH₂), 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. ¹³C 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: ν̄ = 3421 (NH₂), 1622 (C=N) cm⁻¹. C₁₀H₁₅N₃OS (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 Na₂SO₄, filtered, and the solvent was evaporated. The remaining residue was crystallized from Et₂O/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. ¹H NMR: δ = 1.18–1.83 (m, 10 H, cyclohexyl, C₅H₁₀), 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. ¹³C 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: ν̄ = 1773 (C=O) cm⁻¹. C₁₂H₁₉N₃O₂ (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. ¹H NMR: δ = 2.96 [s, 6 H, N(CH₃)₂], 3.56 [s, 2 H, 3,4-(CH₃O)₂-PhCH₂], 3.72 [d, ³J_{H,H} = 1.79 Hz, 6 H, 3,4-(CH₃O)₂-Ph], 6.78–6.80 (m, 1 H, 2'-H), 6.86–6.88 (m, 2 H, 5',6'-H) ppm. ¹³C NMR: δ = 35.58 [3,4-(CH₃O)₂-PhCH₂], 47.66 [N(CH₃)₂], 55.41, 55.52 [3,4-(CH₃O)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: ν̄ = 1773 (C=O) cm⁻¹. C₁₃H₁₇N₃O₃ (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. ¹H 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-Cl₂-PhCH₂), 7.30–7.33 (m, 1 H, 2'-H), 7.56–7.61 (m, 2 H, 5',6'-H) ppm. ¹³C NMR: δ = 20.76 (C-8), 21.02 (C-7,9), 35.00 (3,4-Cl₂-PhCH₂), 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: ν̄ = 1774 (C=O) cm⁻¹. C₁₄H₁₅Cl₂N₃O (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. ¹H NMR: δ = 2.96 [s, 6 H, N(CH₃)₂], 3.66 (s, 2 H, 4-Cl-PhCH₂), 7.31–7.38 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 35.70 (4-Cl-PhCH₂), 48.08 [N(CH₃)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: ν̄ = 1771 (C=O) cm⁻¹. C₁₁H₁₂ClN₃O (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. ¹H NMR: δ = 2.29 (s, 3 H, NCH₃), 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-PhCH₂), 7.32–7.38 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 35.43 (NCH₃), 45.14 (4-Cl-PhCH₂), 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} . $\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{O}$ (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} . $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ (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 $\times$ 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} . $\text{C}_{12}\text{H}_{19}\text{N}_3\text{OS}$ (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, $\text{N}(\text{CH}_3)_2$], 3.73 [d, J = 2.03 Hz, 6 H, 3,4-(CH_3O) $_2$ -Ph], 3.76 [s, 2 H, 3,4-(CH_3O) $_2$ -Ph CH_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) $_2$ -Ph CH_2], 51.68 [$\text{N}(\text{CH}_3)_2$], 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} . $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ (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 -Ph CH_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 -Ph CH_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} . $\text{C}_{14}\text{H}_{15}\text{Cl}_2\text{N}_3\text{S}$ (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, $\text{N}(\text{CH}_3)_2$], 3.86 (s, 2 H, 4- Cl -Ph CH_2), 7.33–7.40 (m, 4 H, 4- Cl -Ph) ppm. ^{13}C NMR: δ = 33.90 (4- Cl -Ph CH_2), 51.32 [$\text{N}(\text{CH}_3)_2$], 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} . $\text{C}_{11}\text{H}_{12}\text{ClN}_3\text{S}$ (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 -Ph CH_2), 7.34–7.40 (m, 4 H, 4- Cl -Ph) ppm. ^{13}C NMR: δ = 34.44 (4- Cl -Ph CH_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} . $\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{S}$ (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} . $\text{C}_{11}\text{H}_{13}\text{N}_3\text{OS}_2$ (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 $\times$ 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.

(4E)-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, $^3J_{\text{H,H}}$ = 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 [$\text{N}(\text{CN})$], 178.52 (C-2), 184.13 (C-4) ppm. IR: $\tilde{\nu}$ = 2193 (CN), 1650 (C=N) cm^{-1} . $\text{C}_{13}\text{H}_{19}\text{N}_5\text{O}$ (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.

(5E)-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, $\text{N}(\text{CH}_3)_2$], 3.72 [s, 2 H, 3,4-(CH_3O) $_2$ -Ph CH_2], 3.73 [d, $^3J_{\text{H,H}}$ = 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) $_2$ -Ph CH_2], 51.32

[N(CH₃)₂], 55.41, 55.50 [3,4-(CH₃O)₂-Ph], 111.91, 113.02 (C-5', C-2'), 114.73 [N(CN)], 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. C₁₄H₁₇N₅O₂ (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.

(4E)-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. ¹H 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-Cl₂-PhCH₂), 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. ¹³C NMR: δ = 20.58 (C-8), 21.64 (C-7,9), 34.20 (3,4-Cl₂-PhCH₂), 61.64 (C-6,10), 115.18 [N(CN)], 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. C₁₅H₁₅Cl₂N₅ (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.

(5E)-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. ¹H NMR: δ = 3.24 [s, 6 H, N(CH₃)₂], 3.83 (s, 2 H, 4-Cl-PhCH₂), 7.34–7.41 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 34.47 (4-Cl-PhCH₂), 51.74 [N(CH₃)₂], 115.08 [N(CN)], 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. C₁₂H₁₂ClN₅ (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.

(4E)-2-(4-Chlorobenzyl)-4-(cyanoimino)-8-methyl-1,3,5,8-tetraaza-spiro[4.5]dec-1-en-5-ium-3-ide (5e): Colourless solid; yield 87% (551 mg), m.p. 250 °C (dec.). ¹H NMR: δ = 2.31 (s, 3 H, NCH₃), 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-PhCH₂), 7.35–7.41 (m, 4 H, 4-Cl-Ph) ppm. ¹³C NMR: δ = 34.18 (4-Cl-PhCH₂), 44.91 (NCH₃), 49.54 (C-7,9), 60.31 (C-6,10), 114.68 [N(CN)], 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. C₁₅H₁₇ClN₆ (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.

(4E)-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. ¹H 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-CH₂), 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. ¹³C NMR: δ = 29.54 (2-thienyl-CH₂), 59.63 (C-7,9), 61.98 (C-6,10), 114.45 [N(CN)], 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. C₁₂H₁₃N₅OS (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.

Acknowledgments

We thank Prof. Dr. J. Kopf for the X-ray crystal structure analysis.

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Received: August 12, 2008
Published Online: October 31, 2008