Studies on Isocyanides and Related Compounds. A Convenient Synthesis of 2,3-Disubstituted Spiroimidazolones

Ricardo Bossio, Stefano Marcaccini*, Sandro Papaleo and Roberto Pepino

CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Dipartimento di Chimica Organica "Ugo Schiff", Universita' di Firenze, via Gino Capponi 9, I-50121 Firenze, Italy

Received September 13, 1993

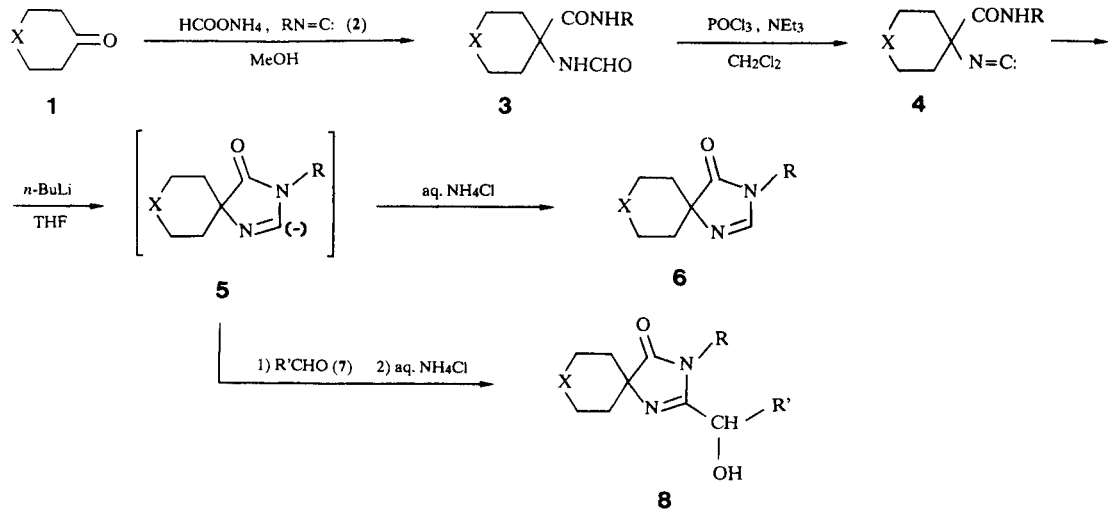
The four-component condensation between cycloketones **1**, ammonium formate, and isocyanides **2** afforded formamides **3**, which were dehydrated to the corresponding isocyanides **4**. Upon treatment with *n*-butyllithium, compounds **4** cyclized to spiroimidazolones **6**, *via* the carbanions **5**. A series of 2,3-disubstituted spiroimidazolones **8** was obtained by reacting **5** with aldehydes **7**.

J. Heterocyclic Chem., **31**, 397 (1994).

In a recent paper [1] it has been reported an improved procedure for the synthesis of spiroimidazolones starting from cyclic ketones, including those bearing heteroatoms, *via* aminonitriles. The above synthetic procedure leads to the formation of spiroimidazolones in which the positions 2 and 3 of the imidazole ring are unsubstituted.

In our continuing research on the synthesis of heterocyclic compounds from isocyanides [2], we reported [3] the synthesis of a series of 3-substituted 1,3-diazaspiro[4.5]dec-1-en-3-ones by cyclizing *N*-substituted 1-isocyano-1-cyclo-

Scheme



1 **3** **4** **5** **6** **8**

1a X = O
b X = S

2a R = C_6H_5
b R = *c*-C_7H_{13}

3, 4, 5, 6a X = O R = C_6H_5
b X = O R = *c*-C_7H_{13}
c X = S R = *c*-C_7H_{13}

7a R' = C_6H_5
b R' = 4-$CH_3C_6H_4$

8a X = O R = C_6H_5 R' = 4-$CH_3C_6H_4$
b X = O R = *c*-C_7H_{13} R' = C_6H_5
c X = O R = *c*-C_7H_{13} R' = 4-$CH_3C_6H_4$
d X = S R = *c*-C_7H_{13} R' = C_6H_5
e X = S R = *c*-C_7H_{13} R' = 4-$CH_3C_6H_4$

hexanecarboxamides which were easily prepared from cyclohexanone *via* Ugi four-component condensation.

In continuation of the above investigation we attempted to prepare a series of 3-substituted spiroimidazolones bearing heteroatoms. As the starting carbonyl compounds we chose the commercially available tetrahydro-4*H*-pyran-4-one (**1a**) and tetrahydro-4*H*-thiopyran-4-one (**1b**). The Ugi four-component condensation between **1**, ammonium formate, and isocyanides **2** afforded compounds **3**, which were dehydrated with phosphorus oxychloride/triethylamine to the corresponding isocyanides **4**. Upon treatment with *n*-butyllithium and subsequent quenching with ammonium chloride, isocyanides **4** were cyclized to spiroimidazolones **6** *via* the intermediate carbanions **5**. The formation of these carbanions offers a further chance for the introduction of substituents in position 2. In fact, upon addition of aldehydes **7** to a solution of **5** a nucleophilic attack on the carbonyl group took place giving the expected alcohols **8**.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Büchi 512 apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide pellets using a Perkin-Elmer 881 spectrophotometer. Proton nmr spectra were determined on a Varian Gemini 200 spectrometer for deuteriochloroform saturated solutions. Elemental analyses were performed using a Perker-Elmer 240 elemental analyzer.

Isocyanides **2a** [4] and **2b** [2c] were prepared according to the literature methods. Tetrahydrofuran was dried over lithium aluminum hydride and distilled prior to use. A 1.6 *M* solution of *n*-butyllithium in hexane from Fluka was employed for all preparations of compounds **6** and **8**.

General Procedure for the Reactions of Carbonyl Compounds **1** with Ammonium Formate and Isocyanides **2**.

A saturated aqueous solution of ammonium formate (3.78 g, 60 mmoles) was added to a solution of the carbonyl compound **1** (30 mmoles) and the isocyanide **2** (30 mmoles) in methanol (60 ml). The resulting solution was refluxed for a variable time and then cooled at −10°. The solid product that separated out was collected by filtration, washed with a little cold methanol and then with ether and air-dried to give **3**. Compounds **3** were employed for the successive reaction without further purification. Analytical samples were obtained from ethanol.

N-Phenyl-4-formylaminotetrahydropyran-4-carboxamide (**3a**).

This compound was obtained (50%) from **1a** and **2a**, reflux time 2 hours, mp 215-216° from ethanol; ir: ν 3288, 1666 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.65; H, 6.31; N, 11.41.

N-Cycloheptyl-4-formylaminotetrahydropyran-4-carboxamide (**3b**).

This compound was obtained (75%) from **1a** and **2b**, reflux time 1 hour, mp 208-209° from ethanol; ir: ν 3293, 1659 cm^{-1}.

Anal. Calcd. for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.02; N, 10.44. Found: C, 62.77; H, 8.79; N, 10.31.

N-Cycloheptyl-4-formylaminotetrahydrothiopyran-4-carboxamide (**3c**).

This compound was obtained (90%) from **1b** and **2b**, reflux time 1 hour, mp 237-238° from ethanol; ir: ν 3295, 1656, 1641 cm^{-1}.

Anal. Calcd. for $C_{14}H_{24}N_2O_2S$: C, 59.12; H, 8.51; N, 9.85. Found: C, 59.30; H, 8.39; N, 10.01.

General Procedure for the Dehydration of Formamides **3** to Isocyanides **4**.

A solution of phosphorus oxychloride (3.25 g, 21 mmoles) in dichloromethane (5 ml) was slowly dropped into a well-stirred suspension of **3** (18 mmoles) and triethylamine (7.16 g, 70 mmoles) in dichloromethane (80 ml), maintaining the temperature at −10°. The reaction mixture was stirred at 0° for 2 hours and then cooled again at −10° and filtered. The filtrate was washed with a saturated aqueous solution of sodium carbonate (6.04 g, 57 mmoles) for 20 minutes. The resulting sludge was filtered and the residue washed with two 25 ml-portions of dichloromethane. The filtrate was washed with 60 ml of water and then with 60 ml of a saturated aqueous solution of sodium chloride. The organic layer was filtered through Celite 545 (Fluka), dried with magnesium sulfate and then evaporated to dryness. The residue was recrystallized from a suitable solvent to give pure **4**.

N-Phenyl-4-isocyanotetrahydropyran-4-carboxamide (**4a**).

This compound was obtained (40%) from **3a**, mp 118-120° from cyclohexane; ir: ν 3379, 2134, 1689 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.70; H, 6.01; N, 12.31.

N-Cycloheptyl-4-isocyanotetrahydropyran-4-carboxamide (**4b**).

This compound was obtained (51%) from **3b**, mp 74-75° from cyclohexane/hexane; ir: ν 3349, 2131, 1656 cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.32; H, 8.91; N, 10.96.

N-Cycloheptyl-4-isocyanotetrahydrothiopyran-4-carboxamide (**4c**).

This compound was obtained (68%) from **3c**, mp 108-110° from cyclohexane; ir: ν 3346, 2126, 1656 cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}N_2OS$: C, 63.12; H, 8.33; N, 10.52. Found: C, 63.26; H, 8.09; N, 10.56.

General Procedure for the Cyclization of Isocyanides **4** to Spiroimidazolones **6**.

A solution of *n*-butyllithium (3.6 mmoles) in hexane was slowly dropped into a well-stirred solution of **4** (3.3 mmoles) in 50 ml of anhydrous THF, maintaining the temperature at −60°. The resulting mixture was stirred, without removing the cooling bath, until the temperature rose to 0° and then neutralized with 10% acqueous ammonium chloride. The reaction mixture was evaporated to dryness and the residue stirred with 30 ml of methylene chloride and 10 ml of water. The organic layer was separated, dried with sodium sulfate, and evaporated to dryness. The residue was recrystallized from a suitable solvent to give **6**.

3-Phenyl-1,3-diaza-7-oxaspiro[4.5]dec-1-en-4-one (**6a**).

This compound was obtained (80%) from **4a**, mp 167-169° from ethanol/water; ir: ν 1730 cm^{-1}; ^1H nmr: δ 1.49-2.21 (m, 4 H, OCH_2CH_2), 3.88-4.10 (m, 4 H, OCH_2), 7.30-7.51 (m, 5 H, ArH), 8.04 (s, 1 H, H-2).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.55; H, 6.29; N, 12.28.

3-Cycloheptyl-1,3-diaza-7-oxaspiro[4.5]dec-1-en-4-one (**6b**).

This compound was obtained (84%) from **4b**, mp 136-138° from cyclohexane; ir: ν 1708 cm^{-1}; ^1H nmr: δ 1.30-2.06 (m, 16 H, H cycloheptane + OCH_2CH_2), 3.81-4.01 (m, 5 H, H-1 cycloheptane + OCH_2), 7.76 (s, 1 H, H-2).

Anal. Calcd. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.25; H, 8.98; N, 11.00.

3-Cycloheptyl-1,3-diaza-7-thiaspiro[4.5]dec-1-en-4-one (**6c**).

This compound was obtained (86%) from **4c**; mp 143-144° from cyclohexane; ir: ν 1707 cm^{-1}; ^1H nmr: δ 1.36-2.21 (m, 16 H, H cycloheptane + SCH_2CH_2), 2.62-3.10 (m, 4 H, SCH_2), 3.82-3.94 (m, 1 H, H-1 cycloheptane), 7.74 (s, 1 H, H-2).

Anal. Calcd. for $C_{14}H_{22}N_2OS$: C, 63.12; H, 8.33; N, 10.52. Found: C, 63.19; H, 8.52; N, 10.73.

General Procedure for the Reaction of Carbanions **5** with Aldehydes **7**.

A solution of *n*-butyllithium (3.6 mmoles) in hexane was slowly dropped into a well-stirred solution of **4** in 50 ml of anhydrous THF, maintaining the temperature at −60°. The resulting mixture was stirred at −35-−40° for 1 hour and then cooled again at −60°. A solution of the aldehyde **7** (3.6 mmoles) in anhydrous THF (7 ml) was added to the above mixture, maintaining the temperature below −50°. The reaction mixture was stirred, without removing the cooling bath, until the temperature rose to 15° and then neutralized with 10% aqueous ammonium chloride. Removal of the solvent left a residue which was stirred with 30 ml of dichloromethane and 10 ml of water. The organic layer was dried with sodium sulfate and evaporated to dryness. The residue was recrystallized from a suitable solvent to give **8**.

2-(4-Methylphenyl)hydroxymethyl-3-phenyl-1,3-diaza-7-oxaspiro-[4.5]dec-1-en-4-one (**8a**).

This compound was obtained (68%) from **4a** and **7b**, mp 162-164° from ethanol; ir: ν 3368, 1713 cm^{-1}; ^1H nmr: δ 1.51-2.18 (m, 4 H, OCH_2-CH_2), 2.28 (s, 3 H, CH_3), 4.01-4.09 (m, 4 H, OCH_2), 4.41 (d, 1 H, J = 6.0 Hz, OH), 5.26 (d, 1 H, J = 6.0 Hz, C*H*OH), 6.74-7.34 (m, 9 H, ArH).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 72.09; H, 6.20; N, 8.21.

3-Cycloheptyl-2-phenylhydroxymethyl-1,3-diaza-7-oxaspiro[4.5]-dec-1-en-4-one (**8b**).

This compound was obtained (75%) from **4b** and **7a**, mp 152-154° from cyclohexane; ir: ν 3319, 1721 cm^{-1}; ^1H nmr: δ 0.83-2.11 (m, 16 H, H cycloheptane + OCH_2CH_2), 3.21-3.42 (m, 1 H, H-1 cycloheptane), 3.88-4.00 (m, 4 H, OCH_2), 4.93 (d, 1 H, J = 3.7 Hz, OH), 5.46 (d, 1 H, J = 3.7 Hz, C*H*OH), 7.30-7.44 (m, 5 H, ArH).

Anal. Calcd. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.71; H, 8.06; N, 7.99.

3-Cycloheptyl-2-(4-methylphenyl)hydroxymethyl-1,3-diaza-7-oxaspiro[4.5]dec-1-en-4-one (**8c**).

This compound was obtained (77%) from **4b** and **7b**, mp 176-178° from ethanol/water; ir: ν 3346, 1692 cm^{-1}; ^1H nmr: δ 0.87-2.10 (m, 16 H, H cycloheptane + OCH_2CH_2), 2.35 (s, 3 H, CH_3), 3.32-3.44 (m, 1 H, H-1 cycloheptane), 3.93-4.00 (m, 4 H, OCH_2), 4.95 (d, 1 H, J = 5.5 Hz, OH), 5.42 (d, 1 H, J = 5.5 Hz, C*H*OH), 7.16-7.26 (m, 4 H, ArH).

Anal. Calcd. for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.19; H, 8.10; N, 7.70.

3-Cycloheptyl-2-phenylhydroxymethyl-1,3-diaza-7-thiaspiro[4.5]-dec-1-en-4-one (**8d**).

This compound was obtained (72%) from **4c** and **7a**, mp 132-133° from cyclohexane; ir: ν 3431, 1724 cm^{-1}; ^1H nmr: δ 0.82-2.14 (m, 16 H, H cycloheptane + SCH_2CH_2), 2.65-3.21 (m, 4 H, SCH_2), 3.30-3.42 (m, 1 H, H-1 cycloheptane), 4.87 (d, 1 H, J = 5.4 Hz, OH), 5.43 (d, 1 H, J = 5.4 Hz, C*H*OH), 7.32-7.42 (m, 5 H, ArH).

Anal. Calcd. for $C_{21}H_{26}N_2O_2S$: C, 67.71; H, 7.58; N, 7.52. Found: C, 67.49; H, 7.66; N, 7.61.

3-Cycloheptyl-2-(4-methylphenyl)hydroxymethyl-1,3-diaza-7-thiaspiro[4.5]dec-1-en-4-one (**8e**).

This compound was obtained (79%) from **4c** and **7b**, mp 164-166° from ethanol/water; ir: ν 3455, 1739 cm^{-1}; ^1H nmr: δ 0.86-2.11 (m, 16 H, H cycloheptane + SCH_2CH_2), 2.34 (s, 3 H, CH_3), 2.62-3.20 (m, 4 H, SCH_2), 3.35-3.39 (m, 1 H, H-1 cycloheptane), 4.90 (d, 1 H, J = 5.5 Hz, OH), 5.40 (d, 1 H, J = 5.5 Hz, C*H*OH), 7.15-7.30 (m, 4 H, ArH).

Anal. Calcd. for $C_{22}H_{30}N_2O_2S$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.21; H, 7.98; N, 7.28.

REFERENCES AND NOTES

[1] C. del Campo and E. F. Llama, *Org. Prep. Proced. Int.*, **22**, 514 (1990).

[2a] R. Bossio, S. Marcaccini, R. Pepino, C. Polo and T. Torroba, *Heterocycles*, **31**, 1287 (1990); [b] R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 1107 (1991); [c] R. Bossio, S. Marcaccini, P. Paoli, R. Pepino and C. Polo, *Synthesis*, 999 (1991); [d] R. Bossio, S. Marcaccini, R. Pepino, P. Paoli and C. Polo, *J. Heterocyclic Chem.*, **30**, 575 (1993).

[3] R. Bossio, S. Marcaccini, P. Paoli, S. Papaleo, R. Pepino and C. Polo, *Liebigs Ann. Chem.*, 843 (1991).

[4] W. P. Weber, G. W. Gokel and I. Ugi, *Angew. Chem.*, **84**, 587 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 530 (1972).