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Polycyclic N-heterocyclic compounds. Part 61: A novel Truce–Smiles type rearrangement reaction of 4-(2-cyanovinyloxy)butanenitriles to give cycloalkeno[1,2-*d*]furo[2,3-*b*]pyridines ☆

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ABSTRACT

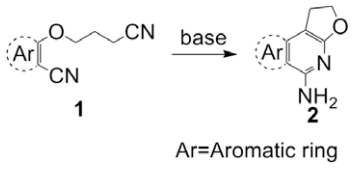
The cycloalkeno[1,2-*d*]furo[2,3-*b*]pyridine skeleton was conveniently synthesized from fused 4-(2-cyanovinyloxy)butanenitriles in one step through sequential intramolecular Michael addition, β-elimination and intramolecular nucleophilic addition. This sequence thus consists of a novel Truce–Smiles type rearrangement followed by cyclization. The 5-amino derivatives were transformed further to lactams in good yields.

1. Introduction

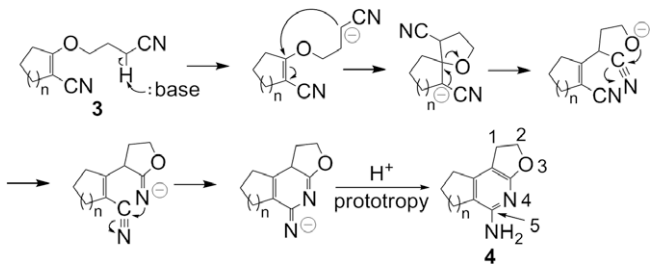
Rearrangement reactions are powerful tools in organic synthesis because simple, readily obtained precursors frequently produce molecules of much higher complexity. Among the many name rearrangement reactions that have been developed is the Truce–Smiles rearrangement, a useful procedure that involves formation of carbon–carbon bonds of an aryl ring with concomitant breaking of a carbon–heteroatom bond.[2,3]

As a part of our continuing program on the synthesis of polycyclic N-heterocyclic compounds for medicinal applications, we have developed a general one step preparation of aromatic ring-fused furo[2,3-*b*]pyridines (**2**) from aryl-1-carbonitriles having a 3-cyanopropoxy group adjacent to the cyano (carbonitrile) group (**1**). This transformation of **1** to **2** is carried out by the action of potassium *tert*-butoxide on **1** and corresponds to a Truce–Smiles rearrangement reaction followed by an intramolecular cyclization (Scheme 1).[4–7]

We have now explored the extension of this reaction sequence to 2-(3-cyanopropoxy)cycloalkene-1-carbonitriles (**3**). One can assume that a base-generated carbanion nucleophile adjacent to a nitrile group will undergo Michael addition (Scheme 2). If β-elimination takes place, the resulting oxyanion could be trapped by intramolecular nitrile groups sequentially to give 5-aminocycloalkeno[1,2-*d*]furo[2,3-*b*]pyridines (**4**). A Truce–Smiles rearrangement



Scheme 1.



Scheme 2.

☆ See Ref. 1.

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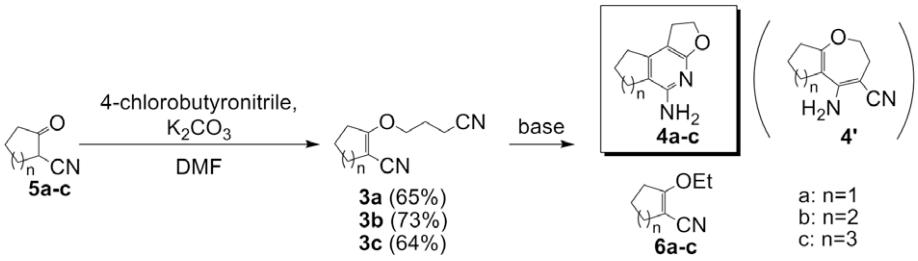


Scheme 3.

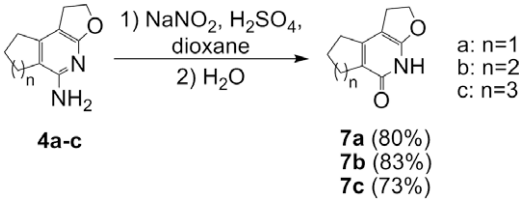
occurs by an intramolecular nucleophilic aromatic substitution at an ipso position,[2] but to date there has been no precedent for this type of rearrangement for aliphatic alkenes such as **3**. We wish to report herein the details of a novel Truce–Smiles type rearrangement reaction for a series of cycloalkenyl substrates **3**.

2. Results and discussion

The starting 2-oxocycloalkanecarbonitriles (**5a**–**c**) were readily prepared from the corresponding commercially available alkanedicarbonitriles by Thorpe–Ziegler condensation, followed by an acid hydrolysis of the resulting enamine.[8,9] Reaction of **5** with 4-chlorobutyronitrile in the presence of potassium carbonate in DMF gave 2-(3-cyanopropoxy)cycloalkene-1-carbonitrile (**3a**–**c**) in moderate yield (Scheme 3). In the IR spectrum of **3**, two cyano absorption bands at 2200–2270 cm^{-1} appeared and the carbonyl band disappeared, strongly suggesting that **3** is an *O*-alkyl rather than a *C*-alkyl derivative.

The initial attempt to react **3a** with potassium *tert*-butoxide in dioxane at reflux temperature gave **4a** as a sole product in 18% yield (Table 1, run 1). In the ^1H NMR spectrum of **4a**, two methylene protons of the dihydrofuran appeared at 3.04 and 4.55 ppm as triplet with a coupling constant 8.6 Hz. The two deuterium oxide exchangeable protons of the amino group appeared at 4.12 ppm. In the IR spectrum of **4a**, amino bands at 3500 and 3350 cm^{-1} were present and the cyano band had disappeared. These data are consistent with the structure of **4a** and were supported by FAB-MS and elemental analysis. The relative low yield may be due to the harsh reaction conditions, but attempting the reaction at a more moderate temperature of 80 °C for 48 h gave only recovered starting material. Changing the base from potassium *tert*-butoxide to NaH gave no improvement in the product yield (run 2) but a solvent change from dioxane to 1,2-dimethoxyethane (DME) gave a slightly improved yield of **4a** (25%) (run 3). When sodium ethoxide was used as a base in ethanol, the cyanopropoxy group was simply substituted with ethoxide to give 2-ethoxycyclopentene-1-carbonitrile (**6a**)[10] in 33% yield. Similar results were obtained for **3b** (runs 5–8) and **3c** (runs 9–12), respectively. The best yields were obtained when NaH was used as base in DME under reflux condition. In none of the reactions did we detect the Thorpe–Zieglar reaction product, that is, 5-amino-2,3-dihydrocycloalkeno[1,2-*b*]oxepin-4-carbonitrile (**4'**). Thus we have demonstrated a novel sequence for cyanovinyl ether (**3**) that involves a Truce–Smiles type rearrangement followed by an intramolecular cyclization.

We next explored transformation of the amino group of **4** to lactam **7** for further derivatization at the 5-position. Thus, **4a** was diazotized with sodium nitrite in dioxane/sulfuric acid and then treated with water (Scheme 4). The amino group of **4a** was easily transformed to the hydroxy group under these conditions and the tautomeric lactam (**7a**) was isolated in 80%. In the ^1H NMR spectrum of **7a**, one deuterium oxide exchangeable lactam proton appeared at 10.44 ppm and the amino group disappeared. In the IR spectrum of **7a**, lactam bands at 3440 cm^{-1} (NH) and 1640 cm^{-1} (CO) were present and the amino band had disappeared. Similar reactions were performed with **4b** and **4c** to give **7b** (83%) and **7c** (73%), respectively.[11] Finally, the bronchodilatory activities of **4** and **7** were evaluated on the basis of their relaxation activity to tracheal contraction induced by carbamylcholine chloride as a primary in vitro assay.[12] None of the compounds showed promising activity.



Scheme 4.

Table 1
Reaction of dinitriles **3** with bases

Run	Compd	Base (1.4–1.5 equiv)	Solvent	Time (h)	Product	Yield (%)
1	**3a**	*tert*-BuOK	Dioxane	2	**4a**	18
2	**3a**	NaH	Dioxane	2	**4a**	18
3	**3a**	NaH	DME	10	**4a**	25
4	**3a**	NaOEt*	Ethanol	6	**6a**	33
5	**3b**	*tert*-BuOK	Dioxane	3	**4b**	15
6	**3b**	NaH	Dioxane	2	**4b**	15
7	**3b**	NaH	DME	8	**4b**	43
8	**3b**	NaOEt*	Ethanol	6	**6b**	37
9	**3c**	*tert*-BuOK	Dioxane	3	**4c**	15
10	**3c**	NaH	Dioxane	2	**4c**	15
11	**3c**	NaH	DME	8	**4c**	21
12	**3c**	NaOEt*	Ethanol	6	**6c**	31

All reactions were carried out under reflux condition.
* 2 equiv was used.

3. Conclusion

In summary, reaction of 2-(3-cyanopropoxy)cycloalkene-1-carbonitrile (**3**) with a base gave 5-aminocycloalkeno[1,2-*d*]furo[2,3-*b*]pyridines (**4**) via a Truce–Smiles type rearrangement followed by an intramolecular cyclization. We are currently exploring their further derivatization at the 5-position for development of potential pharmaceutics.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol was used as a matrix. The IR spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer or FT/IR-200 spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Hitachi R-1500, Varian VXR-200 or VXR-500 instrument each operating at 60, 200, and 500 MHz with tetramethylsilane as an internal standard. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck) or silica gel 70FM (Wako).

4.2. General procedure of 2-(3-cyanopropoxy)cycloalkene-1-carbonitrile (3)

To a solution of 2-oxocycloalkanecarbonitriles **5** (0.120 mol) in dry DMF (400 mL) were added 4-chlorobutyronitrile (15.4 g, 0.149 mol) and potassium carbonate (51.4 g, 0.372 mol) and the mixture was then stirred at 80 °C for 6 h. After the evaporation of the solvent in vacuo, 400 mL of ice water was poured into the residue and the aqueous solution was extracted with ethyl acetate (300 mL × 3). The organic layer was washed with sat. brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel. The eluate of benzene–ethyl acetate (4:1) was evaporated in vacuo to give a viscous pale yellow oil (**3**). **3a** (65%); IR ($CHCl_3$): 2250, 2200 (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 1.94 (2H, quint, J = 7.6 Hz, H-4), 2.09 (2H, quint, J = 6.1 Hz, H-2'), 2.46–2.66 (6H, m, H-3, 5, and CH_2CN), 4.41 (2H, t, J = 6.1 Hz, OCH_2); FABMS: *m/z* 177 (MH^+); FABHRMS *m/z*: Calcd. for $C_{10}H_{13}N_2O$: 177.1028. Found: 177.1037. **3b** (73%); IR ($CHCl_3$): 2270, 2220 (CN); ^1H NMR (60 MHz, $CDCl_3$): δ 1.50–2.00 (6H, m, H-4, 5, and 2'), 2.00–2.45 (4H, m, H-3 and 6), 2.59 (2H, t, J = 5.6 Hz, CH_2CN), 4.12 (2H, t, J = 5.6 Hz, OCH_2); FABMS: *m/z* 191 (MH^+); FABHRMS *m/z*: Calcd. for $C_{11}H_{15}N_2O$: 191.1184. Found: 191.1203. **3c** (64%); IR ($CHCl_3$): 2250, 2210 (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 1.45–1.85 (8H, m, H-4, 5, 6, and 2'), 1.80–2.15 (6H, m, H-3, 7, and CH_2CN), 4.20 (2H, t, J = 5.9 Hz, OCH_2); FABMS: *m/z* 205 (MH^+); FABHRMS: *m/z* Calcd. for $C_{12}H_{17}N_2O$: 205.1341. Found: 205.1351.

4.3. 5-Amino-1,2,7,8-tetrahydro-6*H*-cyclopenta[1,2-*d*]furo[2,3-*b*]pyridine (4a)

To a solution of **3a** (8.00 g, 45.4 mmol) in dry 1,2-dimethoxyethane (DME) (400 mL) was added NaH (1.60 g, 66.7 mmol) and the reaction mixture was then refluxed for 10 h. After the evaporation of the solvent, ice water (400 mL) was poured into the residue and the solution was extracted with ethyl acetate (200 mL × 3). The organic layer was washed with sat. brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was recrystallized from benzene to give **4a** (2.00 g, 25%) as pale brown plates, mp 154–156 °C. IR (KBr): 3500, 3350 (NH); ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (2H, quint, J = 7.0 Hz, H-7), 2.62, 2.75 (each 2H, each t, J = 7.0 Hz, H-6 and 8), 3.04 (2H, t, J = 8.6 Hz, H-1), 4.12 (2H, br s, D_2O exchangeable, NH_2), 4.55 (2H, t, J = 8.6 Hz, H-2); FABMS: *m/z* 177 (MH^+). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.14; H, 6.83; N, 15.64.

4.4. 5-Amino-1,2,6,7,8,9-hexahydrofuro[2,3-*c*]isoquinoline (4b)

To a solution of **3b** (10.0 g, 52.6 mmol) in dry DME (400 mL) was added NaH (1.90 g, 79.2 mmol) and the mixture was refluxed for 8 h under stirring. After the evaporation of the solvent, ice water (400 mL) was added and the aqueous solution was extracted with ethyl acetate (200 mL × 3). The organic layer was washed with sat. brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was recrystallized from benzene to give **4b** (4.30 g, 43%) as pale brown plates, mp 177–179 °C. IR (KBr): 3450, 3350 (NH); ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (4H, m, H-7 and 8), 2.33, 2.53 (each 2H, each t, each J = 5.9 Hz, H-6 and 9), 2.99 (2H, t, J = 8.6 Hz, H-1), 4.17 (2H, br s, D_2O exchangeable, NH_2), 4.55 (2H, t, J = 8.6 Hz, H-2); FABMS: *m/z* 191 (MH^+). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.47; H, 7.28; N, 14.66.

4.5. 5-Amino-1,2,7,8,9,10-hexahydro-6*H*-cyclohepta[1,2-*d*]furo[2,3-*b*]pyridine (4c)

To a solution of **3c** (10.0 g, 49.0 mmol) in dry DME (400 mL) was added NaH (1.70 g, 70.8 mmol) and the mixture was refluxed for 8 h under stirring. After the evaporation of the solvent, ice water (400 mL) was poured into the residue and the solution was extracted with ethyl acetate. The organic layer was washed with sat. brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was recrystallized from benzene to give **4c** (2.10 g, 21%) as pale brown plates, mp 141–143 °C. IR (KBr): 3450, 3350 (NH); ^1H NMR (200 MHz, $CDCl_3$): δ 1.52–1.90 (6H, m, H-7, 8, and 9), 2.53, 2.63 (each 2H, each m, H-6 and 10), 3.07 (2H, t, J = 8.6 Hz, H-1), 4.17 (2H, br s, D_2O exchangeable, NH_2), 4.53 (2H, t, J = 8.6 Hz, H-2); FABMS: *m/z* 205 (MH^+). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.55; H, 7.81; N, 13.60.

4.6. 1,2,4,5,7,8-Hexahydro-6*H*-cyclopenta[1,2-*d*]furo[2,3-*b*]pyridin-5-one (7a)

To a suspension of **4a** (3.00 g, 17.0 mmol) in dioxane (80 mL) and concd H_2SO_4 (0.2 mL) was added dropwise a solution of $NaNO_2$ (2.40 g, 34.8 mmol in 1.5 mL H_2O) with cooling under 5 °C. After the end point of the reaction was confirmed with KI-starch paper, water (200 mL) was poured into the mixture and the solution was stirred at rt for 0.5 h. The precipitated solid was collected on filter in vacuo and recrystallized from dioxane to give **7a** (2.40 g, 80%) as colorless needles, mp 237–239 °C. IR (KBr): 3440 (NH), 1640 (CO); ^1H NMR (500 MHz, DMSO-d_6): δ 2.00 (2H, quint, J = 7.3 Hz, H-7), 2.61, 2.72 (each 2H, each t, each J = 7.3 Hz, H-6 and 8), 3.01 (2H, t, J = 8.6 Hz, H-1), 4.50 (2H, t, J = 8.6 Hz, H-2), 10.44 (1H, br s, D_2O exchangeable, NH); FABMS: *m/z* 178 (MH^+). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.48; H, 6.04; N, 7.84.

4.7. 1,2,4,5,6,7,8,9-Octahydrofuro[2,3-*c*]isoquinolin-5-one (7b)

To a suspension of **4b** (3.00 g, 15.8 mmol) in dioxane (80 mL) and concd H_2SO_4 (0.2 mL) was added dropwise a solution of $NaNO_2$ (2.20 g, 31.9 mmol in 1.5 mL H_2O) under 5 °C. After the end point of the reaction was confirmed with KI-starch paper, water (200 mL)

was poured into the mixture and the solution was stirred at rt for 0.5 h. The precipitated solid was collected by filtration in vacuo and recrystallized from dioxane to give **7b** (2.50 g, 83%) as colorless needles, mp 217–219 °C. IR (KBr): 3480 (NH), 1640 (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.63–1.73 (4H, m, H-7 and 8), 2.30–2.42, 2.44–2.58 (each 2H, each m, H-6 and 9), 2.96 (2H, t, J = 8.6 Hz, H-1), 4.48 (2H, t, J = 8.6 Hz, H-2), 10.55 (1H, br s, D_2O exchangeable, NH); FABMS: m/z 192 (MH^+). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.07; H, 6.81; N, 7.27.

4.8. 1,2,4,5,7,8,9,10-Octahydro-6*H*-cyclohepta[1,2-*d*]furo[2,3-*b*]pyridin-5-one (7c)

To a suspension of **4c** (3.00 g, 14.7 mmol) in dioxane (80 mL) and concd H_2SO_4 (0.2 mL) was added dropwise a solution of $NaNO_2$ (2.00 g, 29.0 mmol in 1.5 mL H_2O) while the solution was cooled under 5 °C. After the end point of the reaction was confirmed with KI-starch paper, water (200 mL) was poured into the reaction mixture which was then stirred at rt for 0.5 h. The precipitated solid was collected on filter in vacuo and recrystallized from dioxane to give **7c** (2.20 g, 73%) as colorless needles, mp 204–206 °C. IR (KBr): 3460 (NH), 1630 (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.36–1.68 (6H, m, H-7, 8, and 9), 2.56–2.68 (4H, m, H-6 and 10), 3.04 (2H, t, J = 8.6 Hz, H-1), 4.46 (2H, t, J = 8.6 Hz, H-2), 10.25 (1H, br s, D_2O exchangeable, NH); FABMS: m/z 206 (MH^+). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.37; H, 7.64; N, 6.88.

Acknowledgments

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References and notes

1. Part 60 Okuda, K.; Tagata, T.; Kashino, S.; Hirota, T.; Sasaki, K. *Chem. Pharm. Bull.* **2009**, *57*, 1296–1299.
2. For a leading review, see Snape, T. J. *Chem. Soc. Rev.* **2008**, *37*, 2452–2458.
3. For recent reports on Truce–Smiles rearrangement, see: (a) Erickson, W. R.; McKennon, M. J. *Tetrahedron Lett.* **2000**, *41*, 4541–4544; (b) Kimbaris, A.; Cobb, J.; Tsakonas, G.; Varvounis, G. *Tetrahedron* **2004**, *60*, 8807–8815; (c) Mitchell, L. H.; Barvian, N. C. *Tetrahedron Lett.* **2004**, *45*, 5669–5671; (d) Snape, T. J. *Synlett* **2008**, 2689–2691.
4. Hirota, T.; Matsushita, T.; Sasaki, K.; Kashino, S. *Heterocycles* **1995**, *41*, 2565–2574.
5. Sasaki, K.; Rouf, A. S. S.; Hirota, T. *J. Heterocycl. Chem.* **1996**, *33*, 49–52.
6. Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* **2001**, *55*, 741–752.
7. Okuda, K.; Yoshida, M.; Hirota, T.; Sasaki, K. *Chem. Pharm. Bull.* **2010**, *58*, in press.
8. Rodríguez-Hahn, L.; Parra, M.; Martínez, M. *Synth. Commun.* **1984**, *14*, 967–972.
9. Liu, H.-J.; Ly, T.-W.; Tai, C.-L.; Wu, J.-D.; Liang, J.-K.; Guo, J.-C.; Tseng, N.-W.; Shia, K.-S. *Tetrahedron* **2003**, *59*, 1209–1226.
10. Lamant, M. *Compt. Rend.* **1959**, *248*, 3714–3716.
11. Compound **7** was also accessible from ethyl 2-(3-cyanopropoxy)cycloalken-1-carboxylate, which was prepared from ethyl 2-oxocycloalkanecarboxylate and chlorobutyronitrile in the presence of K_2CO_3 in DMF, using strong bases directly. But the yield was relatively low (~20%). In this case, intramolecular Claisen type condensation products were not isolated either.
12. Sasaki, K.; Rouf, A. S. S.; Hirota, T.; Nakaya, N. *J. Heterocycl. Chem.* **1999**, *36*, 461–465.