Novel Synthesis of Pyrrolidinones by Cobalt Carbonyl Catalyzed Carbonylation of Azetidines. A New Ring-Expansion–Carbonylation Reaction of 2-Vinylazetidines to Tetrahydroazepinones

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Abstract: Pyrrolidinones can be synthesized in high yields and regioselectivity by the cobalt carbonyl catalyzed carbonylation of azetidines. For 2-substituted azetidines (alkyl, aryl, CH_2OH, CH_2OR, CH_2OCOR, and COOR), carbonyl insertion occurs in the more or less substituted ring carbon–nitrogen bond depending on the kind of substituent group and on the reaction temperature. In the case of 2-vinylazetidines, ring expansion and carbonylation affords seven-membered-ring tetrahydroazepinones. Good functional group tolerance was observed in these reactions.

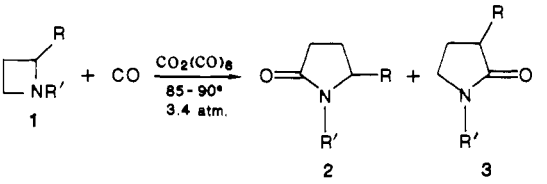
Among the methods available for the synthesis of heterocyclic compounds are those involving the use of transition-metal organometallic complexes as reagents or, much better, as catalysts.[1] A fundamental class of catalytic processes is carbonylation reactions in which carbon monoxide is inserted into an organic substrate, affording a carbonyl-containing product.[2] It is possible to "stitch" carbon monoxide into a strained ring system, resulting in the isolation of a ring-expanded product. In this manner, one can convert 2-arylaziridines to β-lactams in good yields, by simply treating the substrate with carbon monoxide in the presence of a catalytic quantity of a rhodium(I) complex such as chlorodicarbonylrhodium(I) dimer. This reaction is regiospecific and stereospecific, with carbonyl insertion occurring in the more substituted of the two carbon–nitrogen bonds.[3] However, 2-alkylaziridines do not react, even at 30 atm of carbon monoxide.

Four-membered-ring oxetanes and thietanes are carbonylated to the corresponding lactones and thiolactones using cobalt carbonyl or both cobalt and ruthenium carbonyls as catalysts. Alkyl-substituted oxetanes and thietanes do react, but where there is a choice, insertion occurs in the least substituted of the two carbon–heteroatom bonds.[4]

There are no examples, to our knowledge, of the direct transformation of azetidines to pyrrolidinones by metal-catalyzed carbonylation reactions. As azetidines can be easily synthesized by a variety of methods[5] and since a number of pyrrolidinones are of considerable interest, the concept of a metal-catalyzed route to pyrrolidinones is an attractive one, provided the process occurs in good yields and with high regioselectivity. This article reports the attainment of these goals for *both* aryl- and alkylazetidines (in contrast to aziridines), with high regioselectivity for 3- or 5-substituted pyrrolidin-2-ones subject to the nature of the substituent at the 2-position of the substrate and to the reaction temperature. Furthermore, 2-vinylazetidines experience novel carbonylation to the seven-membered-ring tetrahydroazepinones.

Results and Discussion

Reaction of 1-methyl-2-phenylazetidine (**1**, R = Ph, R′ = CH_3) with carbon monoxide and a catalytic amount of cobalt carbonyl (20:1 ratio of **1**/$Co_2(CO)_8$) in benzene, for 24 h at 85–90 °C and 3.4 atm, gave 1-methyl-3-phenylpyrrolidin-2-one (**3**, R = Ph, R′ = CH_3) in 90% isolated yield and traces of isomeric 1-methyl-5-phenylpyrrolidin-2-one (**2**, R = Ph, R′ = CH_3). No reaction occurs in the absence of the metal carbonyl. The observed, exceedingly high regioselectivity is similar to the regiospecificity



encountered in the rhodium(I)-catalyzed carbonylation of 2-arylaziridines.[3] In contrast to the inertness of 2-alkylaziridines, 2-alkylazetidines also undergo cobalt-catalyzed ring expansion to the pyrrolidinone. However, the regioselectivity in these cases is opposite to that found with 1-methyl-2-phenylazetidine, with insertion of carbon monoxide occurring, in all but one instance, only in the least substituted of the two ring carbon–nitrogen bonds Specifically, 1-*tert*-butyl-2-methylazetidine (**1**, R = CH_3, R′ = $C(CH_3)_3$) gave 1-*tert*-butyl-5-methylpyrrolidin-2-one as the only product in 83% yield (reaction with CO and $Co_2(CO)_8$ at 3.4 atm; 95% yield at 1 atm). Similarly, azetidines containing hydroxymethyl, methoxymethyl, and acetoxymethyl substituents all react with CO to form *only* the 5-substituted pyrrolidin-2-ones (**2**, R′ = $C(CH_3)_3$, R = CH_2OH, CH_2OCH_3, CH_2OCOCH_3) in 88–91% yields. The structures of the products were established on the basis of analytical and spectral results (infrared, nuclear magnetic resonance (H-1, C-13 assignments also supported by COSY and HETCOR measurements), and mass spectra—see Table I for data).

Carbonylation of 1-*tert*-butyl-2-(methoxycarbonyl)azetidine (**1**, R = $COOCH_3$, R′ = $C(CH_3)_3$) with $Co_2(CO)_8$ at 90 °C affords the ring-expanded products in 91% yield, the product distribution of **2**/**3** being 97:3. Since this is the one reaction that does afford more than traces of the minor isomer, an examination was made of the influence of temperature, solvent polarity, and catalyst on the isomer distribution. The results in Table II demonstrate the sensitivity of the carbonylation process to the reaction temperature.

At high temperatures (115 °C), only 1-*tert*-butyl-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) is formed, while reducing the temperature to 38 or 43 °C results in the production of an appreciable amount of 1-*tert*-butyl-3-(methoxycarbonyl)-pyrrolidin-2-one (**3**, 41% of the product distribution). However, the increase in **3** (R = $COOCH_3$, R′ = $C(CH_3)_3$) is achieved at the expense of conversion and yield. Nevertheless, the reaction temperature does have a significant influence on the reaction rate and the regioselectivity. The choice of solvent has little effect on the product distribution with polar solvents such as 4-methyl-2-pentanone or *tert*-amyl alcohol, giving **3** (R = $COOCH_3$, R′ = $C(CH_3)_3$) (relative to **2**) in somewhat higher proportion than when a less polar solvent was used (Table III). This is true irrespective of temperature; i.e., one can realize the formation of **2** and **3** in a nearly 1/1 ratio using extended reaction times at 34 °C.

(1) Davidson, J. L.; Preston, P. N. *Adv. Heterocycl. Chem.* **1982**, *30*, 319.
(2) Tkatchenko, I. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergammon Press: Elmsford, NY; 1982; Vol. 8, pp 101–233.
(3) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.
(4) Wang, M. D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.
(5) Moore, J. A.; Ayers, R. S. *Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 2, pp 1–217.

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Table I. $Co_2(CO)_8$-Catalyzed Carbonylation of **1** at 3.4 atm in C_6H_6

R, R′ for **1**	product	yield,[a] %	IR, ν(CO),[b] cm^{-1}	^1H NMR[c] δ ($CDCl_3$)	^{13}C NMR[c] δ ($CDCl_3$)	MS, *m/e*
Ph, CH_3	**3**	90[d]	1698	2.09, 2.46 (m, 2 H, C4 protons), 2.91 (s, 3 H, CH_3), 3.42 (m, 2 H, CH_2N), 3.62 (t, 1 H, J = 8.8 Hz, CHPh), 7.26 (m, 5 H, Ph)	28.04 (CH_3N), 30.16 (C4), 47.72 (C3), 48.05 (CH_2N), 126.81, 127.78, 128.57, 139.91 (Ph carbons), 172.65 (CO)	175 $(M)^+$
	2	traces	1700	2.43–2.77 (m, 4 H, CH_2CH_2), 2.66 (s, 3 H, CH_3), 4.49 (m, 1 H, CHPh), 7.24 (m, 5 H, Ph)		175 $(M)^+$
CH_3, $C(CH_3)_3$	**2**	83	1688	1.25 (d, 3 H, CH_3CH), 1.46 (s, 9 H, $C(CH_3)_3$), 1.60–2.70 (m, 4 H, CH_2CH_2), 3.83 (m, 1 H, $CHCH_3$)	21.88 (CH_3CH), 27.39 (C4), 28.32 ($(CH_3)_3C$), 31.38 (C3), 53.74 ($C(CH_3)_3$), 54.03 (C5), 174.05 (CO)	155 $(M)^+$
CH_2OH, $C(CH_3)_3$	**2**	88[e]	1687	1.42 (s, 9 H, $C(CH_3)_3$), 2.65 (t, 1 H, OH), 1.96–2.05 (m, 2 H, C4 protons), 2.22, 2.52 (m, 2 H, C3 protons), 3.68 (m, 2 H, CH_2O), 3.84 (m, 1 H, C5 proton)	22.80 (C4), 28.42 ($(CH_3)_3C$), 31.80 (C3), 54.13 ($C(CH_3)_3$), 59.77 (C5), 64.22 (CH_2OH), 175.86 (CO)	171 $(M)^+$
CH_2OCH_3, $C(CH_3)_3$	**2**	91[f]	1687	1.41 (s, 9 H, $C(CH_3)_3$), 1.90–2.00 (m, 2 H, C4 protons), 2.18, 2.48 (m, C3 protons), 3.30 (dd, 1 H, CH_2O), 3.34 (s, 3 H, OCH_3), 3.44 (dd, 1 H, CH_2O), 3.86 (m, 1 H, C5 proton)	23.31 (C4), 28.40 ($(CH)_3C$), 31.69 (C3), 53.99 ($C(CH_3)_3$), 57.77 (C5), 59.18 (CH_3O), 74.59 (CH_2O), 175.42 (CO)	185 $(M)^+$
CH_2OCOCH_3, $C(CH_3)_3$	**2**	91	1690, 1745	1.42 (s, 9 H, $C(CH_3)_3$), 1.82–2.10 (m, 2 H, C4 protons), 2.07, (s, 3 H, $OCOCH_3$), 2.23, 2.49 (m, 2 H, C3 protons), 3.95 (m, 3 H, C5 proton and CH_2OCO)	20.91 (CH_3CO), 23.17 (C4), 28.35 ($(CH_3)_3C$), 31.44 (C3), 54.18 ($C(CH_3)_3$), 56.48 (C5), 65.40 (CH_2OCO), 170.5 (OCO), 175.06 (lactam CO)	198 $(M-CH_3)^+$, 140 $(M - CH_2OCOCH_3)^+$
$COOCH_3$, $C(CH_3)_3$	**2**	88[g]	1695, 1740	1.37 (s, 9 H, $C(CH_3)_3$), 1.93, 2.17 (m, 2 H, C4 protons), 2.26, 2.54 (m, 2 H, C3 protons), 3.75 (s, 3 H, OCH_3), 4.35 (m, 1 H, C5 proton)	17.60 (C4), 21.25 ($(CH_3)_3C$), 24.70 (C3), 45.78 (OCH_3), 48.13 ($C(CH_3)_3$), 53.20 (C5), 167.31, 168.76 (carbonyls)	199 $(M)^+$
	3	3	1695, 1740	1.38 (s, 9 H, $C(CH_3)_3$), 2.13, 2.29 (m, 2 H, C4 protons), 3.35–3.43 (m, 2 H, CH_2N), 3.55 (m, 1 H, C3 proton), 3.75 (s, 3 H, $COOCH_3$)	22.20 (C4), 27.64 ($(CH_3)_3C$), 44.32 (C5), 50.17 (C3), 52.5 (OCH_3), 54.60 ($C(CH_3)_3$), 169.69, 170.86 (carbonyls)	199 $(M)^+$
4	**5**	76	1695	1.23–1.73 (m, 8 H, $(CH_2)_4$), 2.09 (m, 1 H, $CHCH_2CO$), 2.30 (m, 2 H, CH_2CO), 2.78 (s, 3 H, NCH_3), 3.54 (m, 1 H, CHN)	20.99, 22.75, 26.91, 27.51 (methylene carbons of cyclohexane ring), 27.09 (CH_3N), 32.23 ($CHCH_2CO$), 37.71 (CH_2CO), 58.66 ($CHNCH_3$)	153 $(M)^+$

[a] Yields are of pure materials. [b] C_6H_6 solution. [c] NMR assignments corroborated by use of COSY and HETCOR techniques. [d] Mp 58–59 °C [lit.[11] mp 58–59 °C]. [e] Mp 86–87 °C. [f] When reaction was effected at 38 °C for 4 days, **2** was obtained as the only product in 13% yield, the remainder being recovered starting material. [g] Mp 82–83 °C.

Table II. Effect of Temperature on $Co_2(CO)_8$-Catalyzed Carbonylation of **1** (R = $COOCH_3$, R′ = $C(CH_3)_3$)[a]

T, °C	reactn time, h	azetidine convsn, %	**2** and **3** yield, %	**2**:**3**
115	24	100	90	100:0
90	24	100	91	97:3
78	43	100	88	93:7
43	168	36	32	59:41
38	168	23	21	59:41

[a] Reaction conditions: 10/1 **1**/$Co_2(CO)_8$, C_6H_6, 3.4 atm of CO.

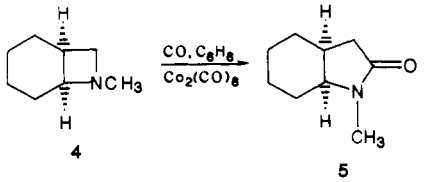
Table III. Effect of Solvent on $Co_2(CO)_8$-Catalyzed Carbonylation of **1** (R = $COOCH_3$, R′ = $C(CH_3)_3$)[a]

solvent	reactn time, h	azetidine convsn, %	**2** and **3** yield, %	**2**:**3**
C_6H_6	43	100	88	93:7
$PhCH_3$	43	100	91	93:7
$CH_3COCH_2CH(CH_3)_2$	48	76	62	85:15
	168[b]	16	13	53:47
tert-amyl alcohol	48	40	36	86:14

[a] Reaction conditions: 10/1 **1**/$Co_2(CO)_8$, 3.4 atm of CO, 78–80 °C. [b] Reaction effected at 34 °C.

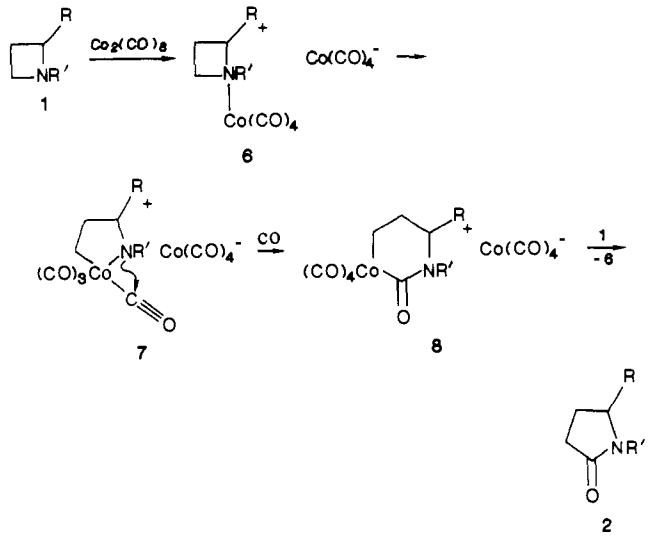
Finally, it should be noted that the use of a $Ru_3(CO)_{12}$–$Co_2(CO)_8$ dual-catalyst system[4] has no effect on the azetidine ring-expansion reaction. In fact, $Ru_3(CO)_{12}$ alone is catalytically inactive. Use of (diphenylacetylene)dicobalt hexacarbonyl as a catalyst for the carbonylation of **1** (R = $COOCH_3$, R′ = CH_3) at 40 °C and 3.4 atm gave **2** and **3** in a 58:42 ratio (20% total yield) after 7 days. Thus, the replacement of the two carbonyl ligands of $Co_2(CO)_8$ by diphenylacetylene has a negligible effect on the reaction.

The ring expansion of azetidines to pyrrolidinones is a stereospecific process. When a 3/1 trans/cis mixture of 1-*tert*-butyl-2,4-dimethylazetidine was exposed to CO in the presence of $Co_2(CO)_8$ for 40 h at 3.4 atm and 120–124 °C, 1-*tert*-butyl-3,5-dimethylpyrrolidin-2-one was formed in 88% yield, with a 3/1 trans/cis isomer distribution. It is interesting to note that, after a reaction time of 23 h, nearly all of the *trans*-azetidine had been converted to the *trans*-pyrrolidinone while 61% of the *cis*-azetidine reacted to form the cis stereoisomer of the pyrrolidinone. In other words, the trans isomer is more reactive than the cis isomer. However, after 40 h, the reaction of both isomers is complete, with the product formed in the noted 3/1 trans/cis ratio. Carbonylation of pure *trans*-1-*tert*-butyl-2,4-dimethylazetidine (we were unable to prepare pure cis reactant) at 1 atm for 20 h gave *trans*-1-*tert*-butyl-3,5-dimethylpyrrolidin-2-one in 20% yield (the remainder being recovered *trans*-azetidine). Compound **4**, another azetidine with stereochemically defined substituents (cis ring junction) reacted, as anticipated, to give 7-methyl-*cis*-7-azabicyclo[4.3.0]nonan-8-one (**5**, 76% yield). The stereochemistry at the ring junction was unaffected, as insertion occurred solely in the least substituted ring C–N bond.



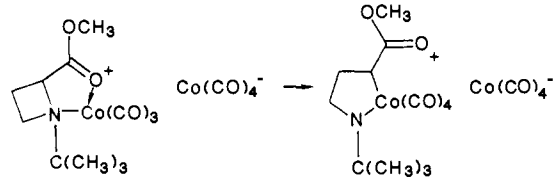
4 **5**

Scheme I



A possible mechanism for the conversion of 2-alkylazetidines (**1**) to 5-substituted pyrrolidin-2-ones (**2**) is outlined in Scheme I. The ionic complex **6** may result from interaction of the substrate with the cobalt catalyst. Insertion of cobalt in the least substituted ring carbon–nitrogen bond would be favored on steric grounds, thus affording the metallacycle **7**. Ligand migration involving the carbon–nitrogen bond rather than the carbon–carbon bond (by analogy with the facility for CO insertion in Pt–N versus Pt–C bonds)[6] may then give **8** which, in the presence of additional azetidine, can collapse to the product with regeneration of **6**.

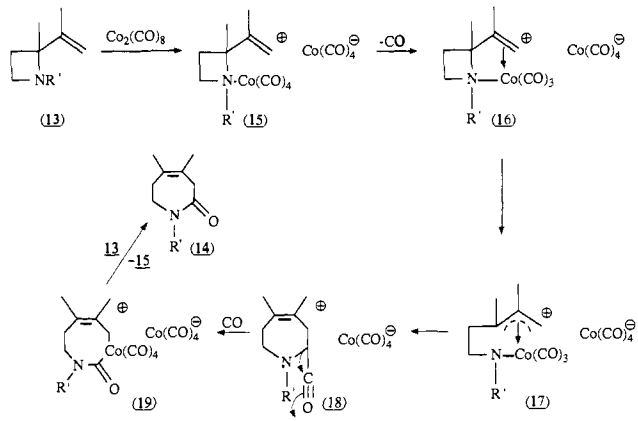
How does one rationalize the results obtained with 1-*tert*-butyl-2-(methoxycarbonyl)azetidine and 1-methyl-2-phenylazetidine? Scheme I can account for the conversion of **1** to **2** (R = $COOCH_3$, R′ = $C(CH_3)_3$). In order to form **3** (R = $COOCH_3$, R′ = $C(CH_3)_3$), it is conceivable that the carbonyl group of the ester function of **6** (R = $COOCH_3$, R′ = $C(CH_3)_3$), rather than being a nonparticipating unit, coordinates to cobalt to give **9**. The driving force for such a reaction may be the formation of a five-membered ring containing cobalt. Such coordination would then direct metal insertion in the more substituted carbon–nitrogen bond of the azetidine ring to give **10**, and ultimately **3**. As oxygen-donor



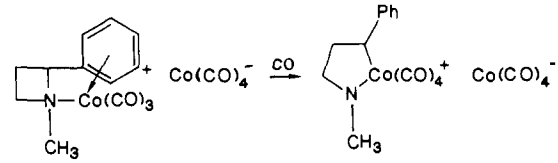
ligand–metal bonds are usually quite fragile,[7] formation of a complex of structural type **9**, as well as its stability, would be enhanced at lower rather than at higher temperatures. This may be why the most favorable conditions for production of **3** (R = $COOCH_3$, R′ = $C(CH_3)_3$) involve the use of temperatures of 34–43 °C rather than 90–120 °C. Azetidines containing hydroxymethyl, methoxymethyl, and acetoxymethyl substituents at the 2-position could also, in principle, form five-membered-ring intermediates involving an oxygen-cobalt donor bond. However, the metallacycle would contain a saturated C–O bond and thus may be less rigid than **9**. This enhanced flexibility could contribute, in a relative sense, to reduced stability, and as a result a route to **2** is more favored than that leading to **3**.

In the case of 1-methyl-2-phenylazetidine, coordination of the π-system of the arene ring to cobalt may generate **11**, which, like

Scheme II

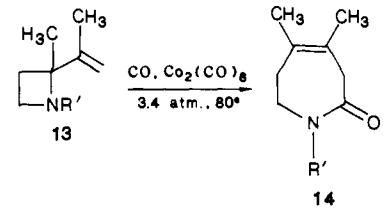


9, could undergo cobalt insertion in the ring C2–N bond to give **12**. One may anticipate that η^2- or π-arene complexation to cobalt



(i.e., **11**) is more robust than oxygen-donor ligand–cobalt complex formation (i.e., **9**). This factor (i.e., relative bond strengths) may be responsible, at least in part, for the observed regioselectivity differences.

If one considers that, in **12**, the arene ring functions as a two-electron donor to the metal, then the $Co_2(CO)_8$-catalyzed reaction of 2-vinylazetidines with carbon monoxide may proceed in an analogous manner to **1** (R = Ph, R′ = CH_3). Reaction did occur for a series of vinylazetidines **13** (R′ = H, $CH_2CH_2COCH_3$, $CH_2CH_2COOCH_3$, and CH_2CH_2CN) but gave 1,2,6,7-tetrahydro-3*H*-azepin-2-ones (**14**) in good yields (see Table IV for data). Optimum conditions for the reaction are the use of a 10:1



ratio of **13**/$Co_2(CO)_8$ in benzene at 80 °C and 3.4 atm of pressure. The products were identified on the basis of analytical and spectral data. It is noteworthy that, in the carbon magnetic resonance spectra of **14**, (R′ = $CH_2CH_2COCH_3$, $CH_2CH_2COOCH_3$, and CH_2CH_2CN), the ring methylene carbon α to nitrogen is deshielded, while that of lactam carbonyl is shielded compared to the signals observed for **14** (R′ = H). These findings are in accord with those reported by Rae[8] for the related hexahydroazepin-2-one system.

A mechanism that accounts for the remarkable ring-expansion–carbonylation reaction of vinylazetidines is presented in Scheme II. Reaction of **13** with $Co_2(CO)_8$ may give the ionic complex **15**, which is analogous to **6**. π-Complexation of the vinyl group to the metal would generate **16**, which can then ring open to form the π-allyl complex **17**. Ring closure under carbon monoxide can give the seven-membered-ring metallacycle **18**. Since no pyrrolidinone was formed in any carbonylation reaction of a 2-vinylazetidine, then the alternate ring closure to form the azametallacyclopentane analogous to **7** is unfavorable here. Conversion of **18** → **19** → **14** parallels that of **7** → **2** (Scheme I).

(6) Bryndza, H. E.; Fultz, W. C.; Tam, W. *Organometallics* **1985**, *4*, 939.
(7) Omae, I. *Coord. Chem. Rev.* **1988**, *83*, 137. Kemmitt, R. D. W.; Russell, D. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Elmsford, NY, 1982; Vol. 5, Chapter 1.

(8) Rae, I. D. *Aust. J. Chem.* **1979**, *32*, 567.

Table IV. Carbonylation of Vinylazetidines (13)

R′ for 13	reaction temp, °C	14 yield,[a] %	mp, °C	IR[b] ν(CO), cm^{-1}	^{1}H NMR[c] δ ($CDCl_3$)	^{13}C NMR[c] δ ($CDCl_3$)	MS, m/e
H	80	52	109–111	1675	1.62 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3), 2.23 (m, 2 H, C6 protons), 3.18 (s, 2 H, C3 protons), 3.38 (t, 2 H, J = 6.1 Hz, C7 protons), 5.85 (s (br), 1 H, NH)	21.10 (CH_3), 22.90 (CH_3), 36.77 (C6), 39.80 (C3), 41.79 (C7), 120.55, 127.55 (olefinic carbons), 175.38 (CO)	139 $(M)^+$
CH_2CH_2-$COCH_3$	50	54	114–115	1658, 1718	1.58 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.14 (s, 3 H, CH_3CO), 2.18 (m, 2 H, C6 protons), 2.74 (t, 2 H, J = 6.6 Hz, CH_2COCH_3), 3.17 (s, 2 H, C3 protons), 3.54 (t, 2 H, J = 6.6 Hz, $NCH_2CH_2COCH_3$)	20.87 (CH_3), 22.84 (CH_3), 30.26 (CH_3CO), 35.58 (C6), 42.61, 42.68, 42.77, 47.49 (other methylene carbons), 121.00, 126.95 (olefinic carbons)	209 $(M)^+$
CH_2CH_2-$COOCH_3$	50 80	60 93		1658, 1738	1.58 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 2.19 (m, 2 H, C6 protons), 2.59 (t, 2 H, J = 6.8 Hz, CH_2COOCH_3) 3.20 (s, 2 H, C3 protons), 3.54 (t, 2 H, J = 5.9 Hz, C7 protons), 3.64 (t, 2 H, J = 6.8 Hz, $CH_2CH_2COOCH_3$), 3.66 (s, 3 H, CH_3)	20.85 (CH_3), 22.83 (CH_3), 33.47 (CH_2COOCH_3), 35.54 (C6), 42.55, 43.39 (C3, NCH_2CH_2CO), 47.29 (C7), 51.75 (OCH_3), 120.99, 126.92 (olefinic protons), 172.36 (carbonyls)	225 $(M)^+$
CH_2CH_2CN	80	86	54–55	1660	1.61 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.28 (m, 2 H, C6 protons), 2.63 (t, 2 H, J = 6.4 Hz, CH_2CN), 3.23 (s, 2 H, C3 protons), 3.62 (t, 2 H, J = 6.4 Hz, NCH_2CH_2CN), 3.63 (t, 2 H, J = 5.9 Hz, C7 protons)	17.32 (CH_2CN), 20.87 (CH_3), 22.87 (CH_3), 35.48 (C6), 42.39 (C3), 44.10 (CH_2CH_2CN), 47.92 (C7), 118.40 (CN), 120.80, 127.05 (olefinic carbons), 173.11 (CO)	192 $(M)^+$

[a] Yields are of pure materials. Satisfactory (±0.4) C, H, N analyses were obtained for new compounds. [b] C_6H_6 solutions. [c] NMR assignments corroborated by use of COSY and HETCOR techniques.

In conclusion, cobalt carbonyl is an effective catalyst for the carbonylation and ring expansion of azetidines to pyrrolidinones. Not only does the reaction display high regio- and stereoselectivities but it can tolerate the presence of functional groups including esters, ethers, and alcohols. Another attractive feature is that the reaction provides a simple entry to an important class of compounds. For instance, 1-methylpyrrolidin-2-ones having methyl or phenyl substituents at the 3- or 5-position possess high antispasmodic activity.[9] Also. 1-methyl-3-phenylpyrrolidin-2-one (**3**, R = Ph, R′ = CH_3) is a valuable precursor to the alkaloid, (±)-desdimethoxymesembrine.[10] The lactam has been prepared in 35–40% yield by phenylation of *N*-methylpyrrolidinone with bromobenzene and lithium isopropylcyclohexylamide.[11] The present methodology provides a high-yield (90%) synthesis of **3** (R = Ph, R′ = CH_3) and, as well, has considerable potential as a versatile route to related pyrrolidin-2-ones (e.g., those with stereochemically defined substituent groups at the 3,4- or 3,5-positions). The transformation of vinylazetidines to tetrahydrazepinones is novel, can tolerate nitrile, ketone, and ester groups, and is promising as a method for the synthesis of interesting azepinones not readily accessible by other means. The chemistry described herein constitutes the first examples of metal-catalyzed carbonylation of azetidines to pyrrolidinones and azepinones.

Experimental Section

General. A Fisher-Johns apparatus was used for melting point determinations. Spectra data were obtained by use of the following spectrometers: Perkin-Elmer 783 (IR), Varian XL-300 or EM-360 (NMR), VG7070E (MS). The organic solvents were dried and distilled by standard methods. Cobalt and ruthenium carbonyls were purchased from Strem Chemcial Co. and were used as received. Elemental analyses were carried out by Guelph Chemcial Laboratories, Guelph, Ontario, and by MHW Laboratories, Phoenix, AZ.

Azetidines. The following azetidines were prepared according to literature procedures: 1-methyl-2-phenylazetidine,[12] 1-*tert*-butyl-2-methylazetidine,[13] 1-*tert*-butyl-2-(methoxycarbonyl)azetidine,[14] 1-*tert*-butyl-2-(hydroxymethyl)azetidine,[15] 1-*tert*-butyl-2-(acetoxymethyl)azetidine,[16] and 7-methyl-*cis*-7-azabicyclo[4.2.0]octane.[17,18] The other azetidines were obtained in the following manner:

(a) 1-*tert*-Butyl-2-(methoxymethyl)azetidine (1, R = CH_2OCH_3, R′ = $C(CH_3)_3$). This azetidine was prepared in 83% yield by reaction of 1-*tert*-butyl-2-(hydroxymethyl)azetidine with 1.5 equiv of sodium hydride (50% dispersion in oil) and methyl iodide in tetrahydrofuran for 1 h at 50 °C. This procedure has been described by Brown and Barton[19] for the methylation of L(+)-3-phenyl-2-butanol. Purification was effected by column chromatography (silica gel) first using hexane (to remove the oil) and then ether to elute the azetidine. ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9 H, $(CH_3)_3C$), 1.91 (m, 2 H, CH_2 at the 3-position), 3.08 (m, 2 H, CH_2N), 3.32 (s, 3 H, OCH_3), 3.38 (m, 2 H, CH_2O), 3.54 (m, 1 H, CHN); ^{13}C NMR ($CDCl_3$) δ 20.31 (CH_2 at the 3-position), 25.18 ($(C-H_3)_3C$), 43.62 (CH_2N), 52.99 ($C(CH_3)_3$), 58.04 (CHN), 59.09 (CH_3O), 78.24 (CH_2O); MS, m/e 157 $(M)^+$.

(b) *cis*- and *trans*-1-*tert*-Butyl-2,4-dimethylazetidine. The procedure described by Freeman and Mondron[13] was followed, except that 3-penten-2-one was used instead of methyl vinyl ketone. Workup by thin-layer chromatography (silica gel) using ethyl acetate as the developer gave the *trans*- and *cis*-azetidines, in a 3:1 ratio, in 81% yield. ^{1}H NMR ($CDCl_3$) δ trans isomer 1.09 (s, 9 H, $(CH_3)_3C$), 1.27 (d, 6 H, J = 6.3 Hz, CH_3CH), 1.80 (t, 2 H, CH_2), 3.89 (m, 2 H, CHN); cis isomer 0.98 (s, 9 H, $(CH_3)_3C$), 1.19 (d, 6 H, J = 6.0 Hz, CH_3CH), 1.53 (m, 2 H, CH_2), 3.26 (m, 2 H, CHN).

(c) 2-Methyl-2-(2-propenyl)azetidine (13, R′ = H). 4-Methyl-4-(2-propenyl)-2-azetidinone,[20] easily obtained by cycloaddition of 2,3-dimethyl-1,3-butadiene with chlorosulfonyl isocyanate followed by alkaline hydrolysis, was treated with lithium aluminum hydride in refluxing ether (N_2 atmsosphere) for 40 h to give pure **13** (R′ = H) in 79% yield. This procedure is superior to that described by Hassner and Wiegand[21] using AlH_3 which did give the desired material but in only 27.1% yield. In fact, these workers reported that $LiAlH_4$ effects reduction of both the carbonyl and olefin groups of the related 4-methyl-4-vinyl-2-azetidinone. However, no such reduction of the carbon–carbon double bond occurs in the

(9) Kiseleva, I. N.; Zubacheva, M. M.; Perekalin, V. V. *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 2236.
(10) Kochhar, K. S.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 4785.
(11) Stewart, J. D.; Fields, S. C.; Kochhar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1987**, *52*, 2110.
(12) Stoilova, V.; Trifonov, L. S.; Orahovats, L. *Synthesis* **1979**, 105.
(13) Freeman, J. P.; Mondron, P. J. *Synthesis* **1974**, 894.
(14) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1968**, *5*, 309.
(15) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 19.
(16) Chen, T. Y.; Hung, M. H.; Chen, P. T.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1179.
(17) Gondos, G.; Lang, K. L.; Szeghy, A.; Dombi, G.; Bermath, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1770.
(18) Moriconi, E.; Mazzochi, P. *J. Org. Chem.* **1966**, *31*, 1372.
(19) Brown, C. A.; Barton, D. *Synthesis* **1974**, 434.
(20) Mickel, S. J.; Hsiao, C. N.; Miller, M. J. *Org. Synth.* **1987**, *65*, 135.
(21) Hassner, A.; Wiegand, W. *J. Org. Chem.* **1986**, *51*, 3652.

Table V. Elemental Analyses of New Compounds

compound	formula	calcd			found		
		C	H	N	C	H	N
2, R = CH_3, R′ = $C(CH_3)_3$	$C_9H_{17}NO$	69.63	11.04	9.02	69.38	11.04	9.27
2, R = CH_2OH, R′ = $C(CH_3)_3$	$C_9H_{17}NO_2$	63.13	10.01	8.18	63.24	10.08	8.24
2, R = CH_2OCH_3, R′ = $C(CH_3)_3$	$C_{10}H_{19}NO_2$	64.83	10.34	7.56	65.06	10.11	7.83
2, R = CH_2OCOCH_3, R′ = $C(CH_3)_3$	$C_{11}H_{19}NO_3$	61.95	8.98	6.57	61.57	9.04	6.66
2, R = $COOCH_3$, R′ = $C(CH_3)_3$	$C_{10}H_{17}NO_3$	60.28	8.60	7.03	60.33	8.40	6.77
3, R = $COOCH_3$, R′ = $C(CH_3)_3$	$C_{10}H_{17}NO_3$	60.28	8.60	7.03	60.57	8.53	7.14
5	$C_9H_{15}NO$	70.55	9.87	9.14	70.15	10.01	9.01
14, R′ = H	$C_8H_{13}NO$	69.03	9.41	10.06	69.12	9.33	10.28
14, R′ = $CH_2CH_2COCH_3$	$C_{12}H_{19}NO_2$	68.87	9.15	6.69	68.71	8.84	6.96
14, R′ = $CH_2CH_2COOCH_3$	$C_{12}H_{19}NO_3$	63.98	8.50	6.22	63.60	8.73	6.20
14, R′ = CH_2CH_2CN	$C_{11}H_{16}N_2O$	68.72	8.39	14.51	69.03	8.61	14.32

reaction of 4-methyl-4-(2-propenyl)-2-azetidinone with $LiAlH_4$.

(d) *N*-(3-Oxobutyl)-2-methyl-2-(2-propenyl)azetidine (13, R′ = $CH_2CH_2COCH_3$), *N*-(2-(Carbomethoxy)ethyl)-2-methyl-2-(2-propenyl)azetidine (13, R′ = $CH_2CH_2COOCH_3$), and *N*-(2-Cyanoethyl)-2-methyl-2-(2-propenyl)azetidine (13, R′ = CH_2CH_2CN). The azetidines **13** (R′ = $CH_2CH_2COCH_3$, $CH_2CH_2COOOCH_3$ and CH_2CH_2CN) were synthesized in 66%, 69%, and 83% yields, respectively, by reaction of **13** (R′ = H) with methyl vinyl ketone, methyl acrylate, and acrylonitrile. Except for replacement of 2-methyl-2-vinylazetidine by 2-methyl-2-(2-propenyl)azetidine, the procedures used were identical with those described in the literature.[21]

13, R′ = $CH_2CH_2COCH_3$: bp 85–87 °C (1.5 mmHg); IR (C_6H_6) ν(CO) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H, CH_3C), 1.72 (s, 3 H, CH_3C=), 1.87–2.27 (m, 2 H, proton at C3 of ring), 2.15 (s, 3 H, CH_3), 2.30–3.13 (m, 5 H, NCH_2CH_2CO and proton at C4 of ring), 3.30 (m, 1 H, proton at C4 of ring), 4.70, 4.83 (m, 2 H, vinyl protons); MS, *m/e* 181 $(M)^+$.

13, R′ = $CH_2CH_2COOCH_3$: bp 75–76 °C (0.2 mmHg); IR (C_6H_6) ν(CO) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H, CH_3C), 1.72 (s, 3 H, CH_3C=), 1.83–2.50 (m, 4 H, protons at C3 of ring and CH_2CO), 2.53–3.06 (m, 3 H, proton at C4 of ring and NCH_2CH_2CO), 3.29 (m, 1 H, proton at C4 of ring), 3.60 (s, 3 H, OCH_3), 4.63, 4.80 (m, 2 H, vinyl protons).

13, R′ = CH_2CH_2CN: bp 73–75 °C (0.6 mmHg); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H, CH_3C), 1.72 (s, 3 H, CH_3C=), 1.78–2.48 (m, 4 H, CH_2CN and protons at C3 of ring), 2.52–3.18 (m, 3 H, NCH_2CH_2CN and proton at C4 of ring), 3.41 (m, 1 H, proton at C4 of ring), 4.69, 4.88 (m, 2 H, vinyl protons); MS(CI), *m/e* 165 $(M + 1)^+$.

General Procedure for the $Co_2(CO)_8$-Catalyzed Carbonylation of Azetidines to Pyrrolidinones. A mixture of the azetidine (1.40 mmol), $Co_2(CO)_8$ (0.024 g, 0.07 mmol), and benzene (4 mL) was placed in a stainless steel autoclave containing a glass liner and a magnetic stirring bar. The autoclave was closed, purged twice with carbon monoxide, and pressurized to 3.4 atm of CO. The reaction mixture was stirred for 24 h at 85–90 °C (oil bath temperature). After the mixture cooled to room temperature, the presure was released slowly, the autoclave was opened, and the brown homogeneous solution was transferred to a vial and allowed to stand in air for 6–12 h, during which time a mauve precipitate (cobalt complex) was formed. The mixture was filtered through a small quantity of Celite, the filtrate was concentrated by rotary evaporation, and the resulting oil was subjected to gas chromatographic analysis. When only one product was present, it was purified by silica gel column chromatography, with $CHCl_3$ as the eluant. When more than one product was formed, purification was achieved by thin-layer chromatography (silica gel) using ether–hexane (85/15) as the developer. See Tables I and IV for yields and spectral data. Analytical data for new compounds are listed in Table V.

Some reactions were also effected at 1 atm of CO (90 °C, 24 h, C_6H_6 or $PhCH_3$ as solvent), and the following results were obtained: **1**, R = Ph, R′ = CH_3, gave **3** in 42% yield; **1**, R = CH_3, R′ = $C(CH_3)_3$, gave **2** in 95% yield; **1**, R = CH_2OH, R′ = $C(CH_3)_3$, gave **2** in 85% yield; **1**, R = CH_2OCH_3, R′ = $C(CH_3)_3$, gave **2** in 92% yield; **1**, R = $COOCH_3$, R′ = $C(CH_3)_3$, gave **2** in 33% yield.

Carbonylation of 1-*tert*-Butyl-2,4-dimethylazetidine. When *trans*-1-*tert*-butyl-2,4-dimethylazetidine was carbonylated for 20 h following the general procedure, *trans*-1-*tert*-butyl-3,5-dimethylpyrrolidin-2-one was isolated in 20% yield: IR (C_6H_6) ν(CO) 1680 cm^{-1}; ^1H NMR ($CDCl_3$, assignments supported by COSY and HETCOR) δ 1.24 (d, 3 H, J = 7.4 Hz, CH_3CHCO), 1.30 (d, 3 H, J = 6.3 Hz, CH_3CHN), 1.41 (s, 9 H, $C(CH_3)_3$), 1.69 (m, 1 H, 1 H of CH_2), 2.33–2.40 (m, 2 H, CHCO and 1 H of CH_2), 3.85 (m, 1 H, *CH*N); ^{13}C NMR ($CDCl_3$) δ 19.20 (CH_3-CHCO), 26.06 (CH_3CHN), 28.33 ((CH_3)$_3$C), 34.24 (CH_2), 37.35 (*CH*-CO), 52.88 (CHN), 53.90 (CN), 177.23 (CO); MS, *m/e* 169 $(M)^+$. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.11; H, 11.03; N, 8.34.

Use of a 3/1 trans/cis mixture of the azetidine for the reaction (40 h, 3.4 atm, 120–124 °C) gave 1-*tert*-butyl-3,5-dimethylpyrrolidin-2-one as a 3/1 trans/cis mixture in 88% yield. The ^1H NMR for the cis isomer (signals for the trans isomer were assigned by comparison with those for the pure trans compound) gave the following signals: δ ($CDCl_3$) 1.12 (d, 3 H, J = 7.0 Hz, CH_3CHCO), 1.21 (d, 3 H, J = 5.9 Hz, J = CH_3CHN), 1.40 (s, 9 H, $C(CH_3)_3$), 1.60–1.84 (m, 2 H, CH_2), 2.54 (m, 1 H, CHCO), 3.80 (m, 1 H, CHN). Anal. Calcd for *cis*- and *trans*-$C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.13; H, 11.24; N, 8.31.

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