Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7287-7290, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01650-4

Chemoselective Intramolecular Aminocarbonylation of Unsaturated Amides under Wacker-type Conditions

Hiroto Harayama, Hirofumi Okuno, Yoshika Takahashi, Masanari Kimura, Keigo Fugami, Shuji Tanaka, and Yoshinao Tamaru*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunnkyo, Nagasaki 852, Japan

Abstract: The Wacker-type aminocarbonylation of unsaturated amides shows distinctive dependence of reactivity on the reaction medium: *endo* nitrogen nucleophiles (*endo*-carbamates **3** and -ureas **5**) undergo aminocarbonylation either in neat methyl orthoacetate (MOA) or in methanol containing AcONa and MOA, while *exo* nitrogen nucleophiles (*exo*-carbamates **1a**, -ureas **1b**, and -sulfonamides **1c**) in methanol (cat. $PdCl_2$, stoichiometric $CuCl_2$ under 1 atm of CO). The generality is indicated by the chemoselective transformations of **7a-d** either into **8a-d** in MOA or into **9a-d** in methanol. Copyright © 1996 Elsevier Science Ltd

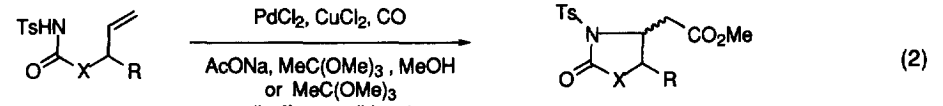
Despite the importance as one of the most efficient and straightforward methods to prepare physiologically important β-amino acid derivatives, the transition-metal catalyzed aminocarbonylation of olefins has not been completely studied.[1]

We reported that nitrogen nucleophiles, depending on the structure types (*endo* and *exo*),[2] displayed completely different reactivities for the Wacker type aminocarbonylation reactions: *exo*-Type nitrogen nucleophiles [*exo*-carbamates **1a**, *exo*-ureas **1b**, and *exo*-tosylamides **1c** (eq 1)] undergo a smooth aminocarbonylation in the presence of $PdCl_2$ under 1 atm of carbon monoxide in methanol at room temperature in the presence of 2-3 equivalents of $CuCl_2$ (*acidic conditions*, since 2 moles of HCl evolve),[3] while *endo*-carbamates **3** are reluctant under the acidic conditions (eq 2; Table 1, run 1): For the aminocarbonylation of **3** to proceed, either sodium acetate (Table 1, run 2) or methyl orthoacetate (run 3), or both (run 4) are required.[4] The role of sodium acetate seemed to be rather apparent, however, that of methyl orthoacetate was unclear: Sodium acetate might work to maintain the acidity of the reaction mixture at an appropriate strength by quenching the HCl evolved, under which the conjugate base of **3**,[5] presumably a reactive intermediate for the aminocyclization of **3**, may be generated and at the same time Pd(0) may be smoothly oxidized to $PdCl_2$ by $CuCl_2$ (*buffer conditions*).

(1)

1a: W = CO_2R, **1b**: W = CONHR, **1c**: W = Ts

2a: W = CO_2R, **2b**: W = CONHR, **2c**: W = Ts



(2)

3: X = O, **5**: X = NH

4: X = O, **6**: X = NH

Here we disclose that methyl orthoacetate (MOA) plays an unexpectedly important role, not only as an additive but also as a solvent, to promote the Wacker-type aminocarbonylation of *endo* nitrogen nucleophiles, *endo*-carbamates **3** and -ureas **5** (eq 2).[6] Furthermore, in this reaction medium only the *endo*-carbamate

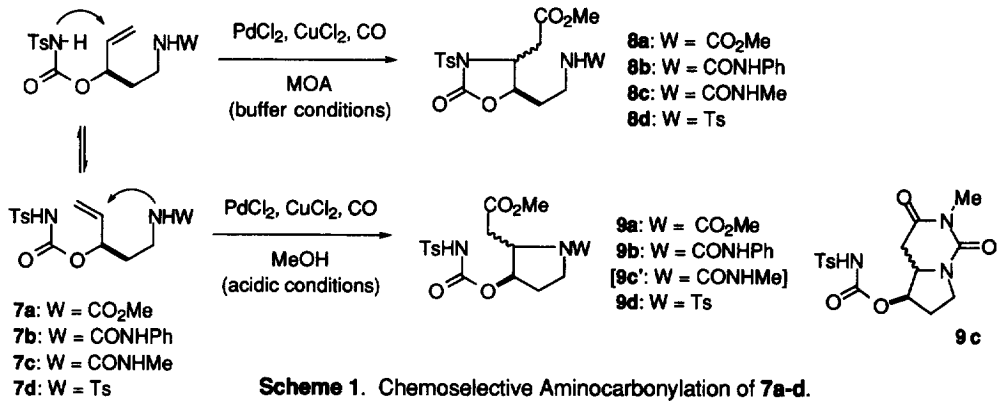
moieties of **7a-d** selectively undergo the aminocarbonylation to provide **8a-d**, respectively (Scheme 1). Under the above mentioned acidic conditions (i.e., in methanol), on the other hand, only the *exo* nitrogen nucleophiles of **7a-d** react selectively to furnish **9a-d**, respectively.

Table 1. Pd^{2+}-Catalyzed Aminocarbonylation of *endo*-Carbamate **3** (R = CH_2CH_2Ph) and *endo*-Urea **5**[a]

run	3 or 5	$PdCl_2$ (equiv)	base (equiv)	additive[b] (equiv)	solvent	temp (°C)/ time (h)	% isolated yield 4 [trans:cis] or 6
1	3	0.25	none	none	MeOH	30/74	4: 0[c,d]
2	3	0.25	AcONa (3.0)	none	MeOH	30/2	4: 43 [3.2:1][d,e]
3	3	0.25	none	MOA (18)	MeOH	30/36	4: 45 [3.6:1][d]
4	3	0.25	AcONa (3.0)	MOA (18)	MeOH	30/8	4: 100 [3.0:1][d]
5	3	0.25	AcONa (3.0)	MOF (18)	MeOH	25/4	4: 94 [3.3:1]
6	3	0.25	AcONa (3.0)	DMP (18)	MeOH	25/4	4: 78 [6.5:1]
7	3	0.25	none	PO (18)	MeOH	25/10	4: 78 [4.1:1]
8	3	0.25	none	none	MOA	25/10→45/2	4: 60 [22:1]
9	5	0.10	none	none	MeOH	35/16	6: 0[f]
10	5	0.25	AcONa (3.0)	none	MeOH	35/6	6: 86
11	5	0.05	none	none	MOA	35/17	6: 81

[a] Reactions were performed under the following conditions, and unless noted otherwise, the conversion of **3** and **5** is 100%: **3** or **5** (1.0 mmol), $PdCl_2$ (indicated amount), $CuCl_2$ (2.3 - 3.0 mmol), and CO (1 atm) in a given solvent (8 ml). [b] MOA: methyl orthoacetate, MOF: methyl orthoformate, DMP: 2,2-dimethoxypropane, PO: propylene oxide. [c] Complex mixture not containing **4** (ca. 90% conversion). [d] Taken from ref. 4b. [e] Isolated yield based on 48% conversion of **3**; no further reaction owing to precipitation of Pd black. [f] Complex mixture of products (6-7 spots on TLC), containing **6** as a minor component (ca. 70% conversion of **5**).

In order to clarify the mechanistic role that MOA plays to promote the cyclization of *endo* nitrogen nucleophiles, we examined the aminocarbonylation of **3** (R = CH_2CH_2Ph) in the presence of compounds that undergo C-O bond cleavage upon contact with HCl (Table 1). Methyl orthoformate (MOF, run 5), 2,2-dimethoxypropane (DMP, run 6), and propylene oxide (PO, run 7) all worked similarly. Surprisingly, when MOA was used as a solvent (Table 1, run 8), the cyclization of **3** proceeded smoothly even in the absence of nucleophilic methanol and furnished *trans*-**4** with the remarkably higher stereoselectivity (*trans*-**4**/*cis*-**4** = 22:1) than the other cases (run 8 vs. runs 2-7).



Scheme 1. Chemoselective Aminocarbonylation of **7a-d**.

endo-Urea **5** showed reaction behavior similar to *endo*-carbamate **3** (eq 2; Table 1, runs 9-11,):[6] The aminocarbonylation of **5** was unsuccessful in methanol and provided an intractable mixture of products (6-7 spots on TLC) containing the expected product **6** as a minor component (Table 1, run 9), while the cyclization of **5** proceeded smoothly either in methanol containing sodium acetate (run 10) or in MOA alone (run 11) to provide **6** in excellent yields.

These results suggest that these ethereal additives (MOA, MOF, DMP, PO), similarly to sodium acetate, serve not only as efficient HCl scavenger but also as bases to generate the conjugate bases of **3** and **5** (buffer conditions). Furthermore, MOA, as a consequence of the reactions with HCl (e.g., $MeC(OMe)_3$ + HCl → $MeC(OMe)_2Cl$ + MeOH), supplies methanol necessary for the methoxycarbonylation of **3** and **5**.

A further distinctive dependence of the reactivity of nitrogen nucleophiles upon the reaction medium was observed when **7**, possessing an *endo*-carbamate moiety together with *exo*-carbamate (**7a**), *exo*-urea (**7b,c**), and *exo*-tosylamide (**7d**) moieties in the same molecules (Scheme 1), were subjected to the aminocarbonylation under three different conditions: (1) in methanol containing sodium acetate and MOA (buffer conditions), (2) in MOA (buffer conditions), and (3) in methanol (acidic conditions). As being apparent from the results summarized in Table 2, under either one of the two buffer conditions only the *endo*-carbamate moieties of **7a-d** reacted selectively to provide 1,3-oxazolidin-2-ones **8a-d**, respectively, in moderate to good yields (runs 1-2, 4-5, 7, 9-10). Of these two buffer conditions, the ones using MOA as a solvent displayed the much higher *trans* selectivities than the other using methanol containing sodium acetate and MOA.

Table 2. Pd^{2+}-Catalyzed Chemoselective Aminocarbonylation of **7a-d**[a,b]

run	**7** (W)	$PdCl_2$ (equiv)	$CuCl_2$ (equiv)	base (equiv)	additive (equiv)[c]	solvent	temp (℃)/ time (h)	% isolated yield **8** [trans:cis]	**9** [trans:cis]
1	**7a**: CO_2Me	0.10	3.0	AcONa (3.0)	MOA (18)	MeOH	25/35	**8a**: 74 [2.8:1]	0
2	**7a**: CO_2Me	0.10	2.3	none	none	MOA	35/7	**8a**: 68 [11:1]	0
3	**7a**: CO_2Me	0.10	3.0	none	none	MeOH	25/120	0	**9a**: 58 [1.2.8]
4	**7b**: CONHPh	0.10	3.0	AcONa (3.0)	MOA (18)	MeOH	25/30	**8b**: 85 [11:1]	0
5	**7b**: CONHPh	0.25	2.3	none	none	MOA	35/6	**8b**: 45 [>30:1]	0
6	**7b**: CONHPh	0.10	3.0	none	none	MeOH	25/120	0	**9b**: 36 [1:3.8]
7	**7c**: CONHMe	0.10	3.0	AcONa (3.0)	MOA (18)	MeOH	25/48	**8c**: 85 [5.2:1]	0
8	**7c**: CONHMe	0.10	3.0	none	none	MeOH	25/22	0	**9c**: 59 [1:1.1]
9	**7d**: Ts	0.10	3.0	AcONa (3.0)	MOA (18)	MeOH	25/17	**8d**: 78 [3.3:1]	0
10	**7d**: Ts	0.25	2.3	none	none	MOA	35/6	**8d**: 50 [20:1]	0
11	**7d**: Ts	0.10	3.0	none	none	MeOH	25/72	0	**9d**: 79 [1:2.9]

[a] For the structures of **7a-d**, **8a-d**, and **9a-d**, see Scheme 1. [b] Reactions were performed by using **7** (1 mmol) in a given solvent (8 ml) under 1 atm of CO. All reactions were complete after the periods of times indicated. [c] MOA: methyl orthoacetate.

The chemoselective transformation of **7a-d** to **8a-d** suggests that sodium acetate and MOA suppress the aminocarbonylation of the *exo* nitrogen nucleophiles. Indeed, in contrast to the previous observation[3b] that in methanol the aminocarbonylation of *exo*-sulfonamide **1c** (R' = H) proceeds smoothly at room temperature and gives rise to **2c** (R' = H) in a quantitative yield, the reaction of **1c** turned out to be very slow when undertaken in methanol containing sodium acetate and MOA and provided **2c** (R' = H) in less than 5% yield with recovery of **1c** in 65% yield (0.25 equivalents of $PdCl_2$, 2.3 equivalents of $CuCl_2$, 3 equivalents of sodium acetate, 18

equivalents of MOA at 35 ℃ for 24 h).

Under acidic conditions, on the other hand, only the *exo* nitrogen nucleophiles of **7a-d** reacted selectively to provide pyrrolidines **9a-d**, respectively. In these cases, the *cis* isomers predominated over the *trans* isomers (Table 2, runs 3,6,8,11).[7] The bicyclic compound **9c** may be formed via an intramolecular imidation of the primary cyclization product **9c'**.[3b] The chemoselective formation of **9a-d** is a natural consequence of the reluctance of *endo*-carbamate moieties of **7a-d** for the aminocarbonylation in methanol (*vide supra*).

In conclusion, *endo* and *exo* nitrogen nucleophiles behave completely differently for the Wacker-type aminocarbonylation. The former is reactive either in neat MOA or in methanol containing sodium acetate and MOA (buffer conditions) and the latter is reactive in methanol (acidic conditions). Therefore, we can conduct the chemoselective aminocarbonylation of **7a-d**, providing either **8a-d** in MOA (or in methanol containing sodium acetate and MOA) or **9a-d** in methanol.[8]

Acknowledgment. We thank Mr. Y. Ohhama, NMR Facility, for his assistance. Support from the Ministry of Education, Science, Sports and Culture, Japanese Government, is acknowledged.

REFERENCES AND NOTES

1. Hegedus, L. S. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp. 559-563.
2. The terms *exo* and *endo* used here are to discriminate two types of nitrogen nucleophiles: for example, *exo*-carbamates (**1a**) are meant to refer to those providing nitrogen heterocycles (e.g., **2a**, eq 1) that possess the carbamate group as the ring substituent and *endo*-carbamates (**3**) are those furnishing heterocycles that contain the carbamate group as the ring component (e.g., **4**, eq 2).
3. (a) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731-5741. (b) Tamaru, Y.; Hojo, M.; Higashimura, J.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994-4002.
4. (a) Kimura, M.; Saeki, N.; Uchida, S.; Harayama, H.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7611-7614. (b) Tamaru, Y.; Tanigawa, H.; Itoh, S.; Kimura, M.; Tanaka, S.; Fugami, K.; Sekiyama, T.; Yoshida, Z. *ibid.* **1992**, *33*, 631-634.
5. Estimated p*K*a of **3** is 4.2: Taylor, L. D.; MacDonald, R. J.; Rubin, E. L. *J. Polym. Sci. Part A-1*, **1971**, *9*, 3059-3063.
6. *N*-Allyl-*N*,*N'*-dialkyl substituted *endo*-Ureas undergo aminocarbonylation smoothly under acidic conditions (i.e., in methanol).[3b]
7. For the similar *cis* selective cyclization, see ref. 3a. See also, Tamaru, Y.; Harayama, H.; Bando, T.; Nagaoka, H.; Yoshida, Z. *Liebigs Ann.* **1996**, 223-234 and references cited therein.
8. Reactions were typically performed as follows: Buffer conditions (Table 2, run 10): A flask charged with **7d** (452 mg, 1 mmol), $PdCl_2$ (44.3 mg, 0.25 mmol), and $CuCl_2$ (309 mg, 2.3 mmol) was purged with CO (a balloon). MOA (8 ml, distilled from Na) was added into the flask via syringe and the heterogeneous mixture was stirred at 35 ℃ for 6 h (no precipitation of palladium black). After dilution with EtOAc (50 ml), the mixture was washed with aq NH_4Cl/NH_3 (5% each, 2 × 15 ml), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (hexane / EtOAc gradient) to provide a mixture of *trans*- and *cis*-**8d** (20:1) in 50% yield. *trans*-**8d**: M.p. 144.5-145.5 ℃ (dichloromethane/hexane); IR (KBr) 3540 (w), 3275 (m), 1785 (s), 1735 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.68-1.92 (m, 2 H), 2.41 (s, 3 H), 2.44 (s, 3 H), 2.80 (dd, J = 9.5, 17.2 Hz, 1 H), 2.99-3.06 (m, 2 H), 3.12 (dd, J = 2.9, 17.2 Hz, 1 H), 3.67 (s, 3 H), 4.34 (dt, J = 2.9, 9.5 Hz, 1 H), 4.41 (ddd, J = 2.9, 5.1, 8.2 Hz, 1 H), 5.21 (t, J = 6.6 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 8.1 Hz, 2 H), 7.90 (d, J = 8.1 Hz, 2 H). $C_{22}H_{26}N_2O_8S_2$: calcd. C 51.76, H 5.13, N 5.49, S 12.55; found C 51.57, H 5.05, N 5.35, S 12.73.

(*Received in Japan* 15 *July* 1996; *revised* 17 *August* 1996; *accepted* 20 *August* 1996)