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A Novel Route to 2,3-Pyrazol-1(5*H*)-ones via Palladium-Catalyzed Carbonylation of 1,2-Diaza-1,3-butadienes

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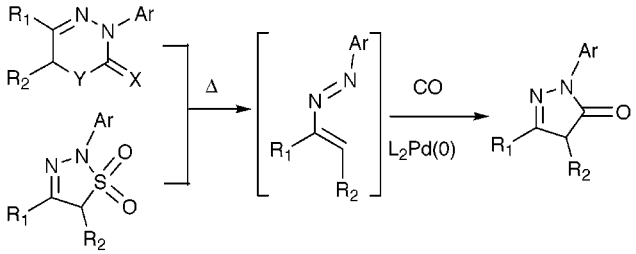
ABSTRACT



A novel Pd(0)-catalyzed carbonylation of both isolable 1,2-diaza-1,3-butadienes and those generated in situ by extrusion of SO_2 and CO_2 from heterocyclic precursors is described. The reaction proceeds at room temperature to 110 °C under 1–2 atm of CO to afford 2,3-pyrazol-1(5H)-ones in good to excellent yields. The effect of catalyst structure and stability on the carbonylation reaction is evaluated.

There is considerable current interest in developing environmentally benign methods for preparation of heterocyclic systems. As a class, 2,3-pyrazol-1(5*H*)-ones **1** have found considerable utility as photographic couplers, pharmaceutical agents, and intermediates.[1,2] Transition metal catalysis potentially offers considerable advantages in terms of simplicity, lower costs, avoidance of the use of toxic reagents such as phosgene, and a reduction in the waste stream. Accordingly, we sought to develop a novel method for preparation of **1** via metal-catalyzed cyclocarbonylation of 1,2-diaza-1,3-butadienes **2**.

Diazabutadienes **2** have been extensively investigated as reactive intermediates (often unisolable) for the preparation of heterocycles principally by nucleophilic addition.[3] Cyclocarbonylation of 1,3-dienes to saturated and unsaturated ketones is known to occur with a variety of metals, including Fe, Ni, and Ti.[4] However, no direct literature precedent existed for the cyclocarbonylation of vinyl azo species such as **2** (Figure 1) except for the early work of Tsuji on the

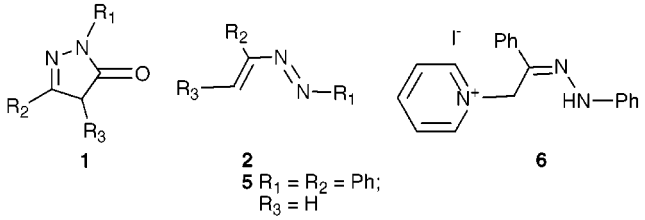


Figure 1.

Pd-catalyzed carbonylation of azobenzene and subsequent studies of the cyclopalladated intermediates.[5]

Thus, we chose to begin our investigation by examination of the palladium-catalyzed carbonylation of the stable, well-characterized monomeric diazabutadiene **3**.[6]

Treatment of a bright red solution of **3** in toluene with 1−10 mol % of Pd(0) catalyst under an atmosphere of CO

(1) (a) Whitaker, A. *J. Soc. Dyers Colour.* **1995**, *111*, 66−72. (b) Furutachi, N. *Nippon Shashin Gakkaishi* **1992**, *55*, 192−8.

(2) Brune, K., Ed. *Agents and Actions Supplements, Vol. 19: 100 Years of Pyrazolone Drugs. An Update*; Birkhaeuser Verlag: Basil, Switzerland, 1986; p 355.

(3) (a) Arcadi, A.; Attanasi, O. A.; De Crescentini, L.; Rossi, E.; Serra-Zanetti, F. *Synthesis* **1996**, 533−6. (b) Arcadi, A.; Attanasi, O. A.; Liao, Z.; Serra-Zanetti, F. *Synthesis* **1994**, 605−8. (c) Schantl, J. G.; Karpellus, P.; Prean, M. *Tetrahedron* **1982**, *38*, 2643−52.

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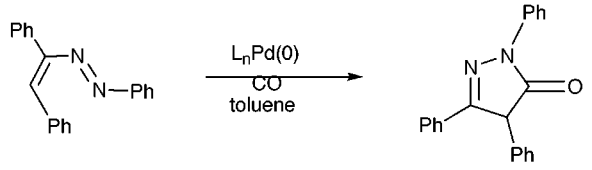
(1−2 atm) at room temperature or 100 °C for 0.15−30 h resulted in the discharge of the red color to afford a colorless to tan solution which ultimately deposited black metallic Pd if heating was continued. Isolation and purification of the organic product afforded generally excellent yields (78−90%) of the desired 2,4,5-triphenyl-2,3-pyrazol-1(5*H*)-one (**4**) (Table 1).

Table 1. Carbonylation of **3**



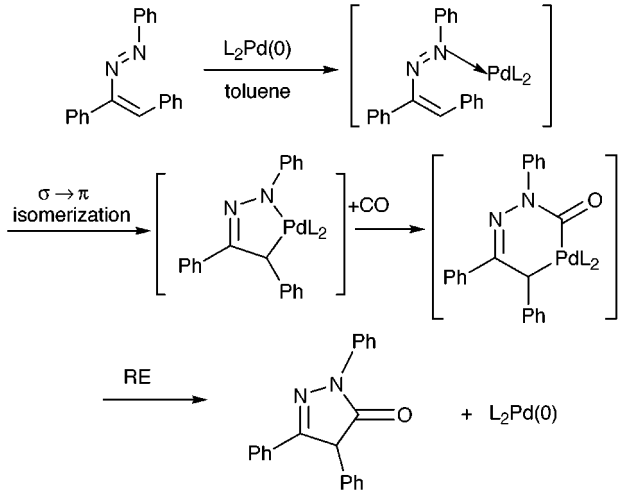
3 **4**

catalyst	mol(%)	CO (atm)	temp (°C)	time (h)	yield (%)
$Pd(PPh_3)_4$	10	2	25	30	81
$Pd(PPh_3)_4$	10	1	100	0.75	78
$Pd(PPh_3)_4$	10	2	100	0.25	90
$Pd(dppe)_2$	1	2	100	4	83
$Pd(PPh_3)_4$	10	1	100	0.67	51[a]

[a] Reaction conducted in acetonitrile.

Although no intermediates were detected, by rough analogy to the cyclopalladation of azobenzene, we surmise that the reaction takes the course shown in Scheme 1.[5] However,

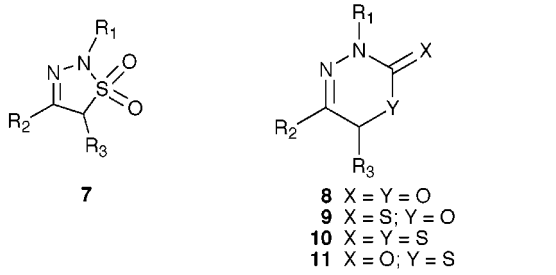
Scheme 1



it is possible that CO enters the ligand sphere of Pd prior to $\sigma \rightarrow \pi$ isomerization and migratory insertion of CO precedes cyclopalladation.

Having verified that the overall transformation is feasible, we attempted to utilize less stable 1,2-diazabutadienes. Attempts to intercept 1,3-diphenyl-1,2-diazabutadiene **5**, by in situ generation of **5** from the pyridinium salt **6**[7] by elimination of pyridine using triethylamine in the presence of CO and $Pd(PPh_3)_4$, failed to afford any of the desired pyrazolone. The only observed product arose from cyclodimerization of the diazadiene intermediate as had been previously documented.[7]

It was evident that the desired carbonylation could not effectively compete with [4 + 2] cycloaddition if the diazadiene was present in high concentration with respect to the Pd(0) catalyst under conditions where the cyclopalladation/carbonylation was slow. Thus, we set out to identify suitable stable precursors for diazadienes which would afford the required intermediates by thermal decomposition under conditions where cyclopalladation/carbonylation would be rapid. We have developed several such precursors in the form of heterocycles **7**−**11**, as described in the preceding Letter (Figure 2).[8]



7

8 X = Y = O
9 X = S; Y = O
10 X = Y = S
11 X = O; Y = S

Figure 2.

This strategy proved successful although optimal conditions (precursor, ligand/catalyst, CO pressure, temperature, and time) must be developed for each substrate owing to the need to match the decomposition rate of the precursor to the rate of cyclopalladation/carbonylation. If the ligand employed is too strongly coordinating at ∼110 °C, a temperature at which the carbonylation generally proceeds efficiently, the diazadiene undergoes dimerization. If the ligand is too weakly bound, the catalyst aggregates and precipitates from solution, prematurely terminating the catalytic cycle.

As shown in Table 2, we began with the triphenyl derivatives **7a**−**9a** since we knew the diazadiene **3** produced upon decomposition of these substrates would (1) not undergo dimerization, (2) undergo carbonylation to **4**, and (3) be stable enough to persist in solution.

(4) (a) Franck-Neumann, M.; Vernier, J. M. *Tetrahedron Lett.* **1992**, *33*, 7365−8. (b) Franck-Neumann, M.; Michelotti, E. L.; Simler, R.; Vernier, J. M. *Tetrahedron Lett.* **1992**, *33*, 7361−4. (c) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450−1. (d) Llebaria, A.; Camps, F.; Moreto, J. M. *Tetrahedron* **1993**, *49*, 125. (e) Thompson, J. M.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 2667−74.

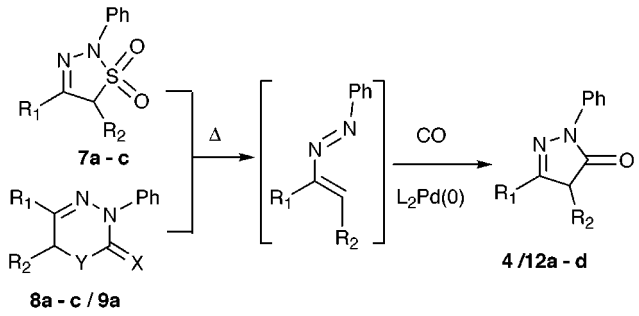
(5) (a) Takahashi, H.; Tsuji, J. *J. Organomet. Chem.* **1967**, *10*, 511−17. (b) Bruce, M. I.; Goodall, B. L.; Stone, F. G. A. *J. Chem. Soc., Chem. Commun.* **1973**, 558−9. (c) Ghedini, M.; Pucci, D.; Crispini, A.; Aiello, I.; Barigelletti, F.; Gessi, A.; Francescangeli, O. *Appl. Organomet. Chem.* **1999**, *13*, 565−81.

(6) Schantl, J.; Karpellus, P. *Monatsh. Chem.* **1978**, *109*, 1081−92.

(7) Schantl, J. *Monatsh. Chem.* **1974**, *105*, 322−6.

(8) Boeckman, R. K., Jr.; Ge, P.; Reed J. E. *Org. Lett.* **2001**, *3*, 3647−3650.

Table 2. In Situ Diene Generation and Carbonylation



starting material	$L_nPd(0)$[a] (mol %)	CO (atm)	temp (°C) time (h)	prdt	yield[b] (%)
7a	$Pd(PPh_3)_4$ (10)	1	100	**4**	78
R_1 = Ph			18		
R_2 = Ph					
7b	$Pd(PPh_3)_4$ (10)	1	100	**12c**	54
R_1 = Ph			18		
R_2 = H					
7c	$Pd(PPh_3)_4$ (10)	1	100	**12d**	74
R_1 = CH_3			18		
R_2 = Ph					
8a	$Pd(dppe)_2$ (5)	2	135	**4**	58
R_1 = Ph			24		
R_2 = Ph					
8b	$Pd(PPh_3)_4$ (10)	1	110	**12a**	62
R_1 = Ph			20		
R_2 = OPh*p*Cl					
8c	$Pd(PPh_3)_4$ (10)	1	110	**12b**	40
R_1 = Ph			20		
R_2 = OPh					
9a	$Pd(dppe)_2$ (5)	2	110	**4**	81
R_1 = Ph			12		
R_2 = Ph					

[a] The catalyst was generated in situ by combination of the appropriate stoichiometry of Pd_2dba_3 with the phosphine or reduction of $Pd(OAc)_2$ by phosphine. [b] Unoptimized.

The oxadiazinone **8a** was examined first. It was noted that rapid decomposition with gas evolution was evident at ~140 °C for **8a**.[8] Thus, **8a** and $Pd(dppe)_2$ (5 mol %) were heated at 135 °C in toluene under CO (2 atm) for 24 h. Isolation and purification of the products afforded the expected pyrazolone **4** in 58% yield.

Our experience with this substrate suggested that the yield-limiting feature of the reaction was the high decomposition temperature of the oxadiazinone **8a** which limited the catalyst lifetime under the reaction conditions. Concurrent work in our laboratory had established that substitution of sulfur for one or more of the oxygen atoms of oxadiazinone **8** had the beneficial effect of lowering the temperature at which decomposition to the diazadiene occurred.[8] The oxadiazinethiones **9** proved optimal, undergoing decomposition at ~50 °C lower than the corresponding oxadiazinone. Treatment of **9a** with CO in the presence of $Pd(dppe)_2$ (5 mol %) at 110 °C for 12 h afforded pyrazolone **4** after purification in 81% yield.

We also examined whether heteroatoms were tolerated at C_5 since derivatives of this type can have particular utility.[1] Oxadiazinone **8b** was carbonylated at 110 °C using $Pd(PPh_3)_4$ (Table 2) and afforded the expected pyrazolone **12a** in 62% yield. When the related aryloxy derivative **8c** was employed, the yield of **12b** diminished to 40%. On the basis of control experiments, we attribute the lower yields in these cases to decreased catalyst and product stability resulting from the extended reaction time.

The thiadiazole dioxides **7** proved to be generally more reactive substrates, undergoing thermal decomposition between 90 and 110 °C.[8] Thus, **7a** was carbonylated in CO-saturated hot toluene solution (110 °C) in the presence of $Pd(PPh_3)_4$ generated in situ from $Pd(OAc)_2$ and 4 equiv of PPh_3. This procedure afforded pyrazolone **4** in 78% yield, comparable to that obtained from the diene **3** under similar conditions. Derivatives lacking a C_5 substituent bearing both C_4 aryl and alkyl substituents were prepared using this procedure. Similar treatment of **7b** and **7c** under the conditions described above for the triphenyl derivative afforded the expected pyrazolones **12c** and **12d** in 54% and 74% yields, respectively.

Further work is necessary to establish the optimal ligands and reaction conditions for efficient formation of pyrazolones possessing wide structural diversity. However, clearly catalytic cyclocarbonylation of thermally generated 1,2-diazabutadienes provides a new and potentially useful route to 2,3-pyrazol-1(5*H*)-ones.

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Supporting Information Available: General experimental procedures and characterization data for **4**, **12a**, **12b**, **12c**, and **12d**. This information is available free of charge via the Internet at http://pubs.acs.org.

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