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Free Radical Cyclizations Leading to Nitrogen Heterocycles. II. 2-Phenylpyrazolidin-3-ones via Tributyltin Hydride Reaction With Alpha-bromoacylated Phenylhydrazones

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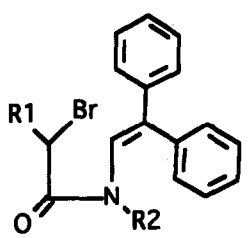
Abstract: The unexpected observation of 2-phenylpyrazolidin-3-one formation during an attempted 4-exo Trig cyclization of an a-bromoacylated phenylhydrazone is a general reaction.

Free radical cyclization chemistry provides an efficient strategy for construction of carbocyclic and heterocyclic molecular frameworks.[1] Tandem all-carbon cyclizations,[2] butyrolactone formation,[3] and γ-lactam generation[4] provide representative examples of recent on-going studies. Also intriguing is the ability of α-bromo enamide substrates (*e.g.* **1a**,...,**1d**) to produce β-lactams (**2a**,...,**2d**) upon reaction with tributyltin hydride.[5] This suggests the possibility that other related functionality (*e.g.* oximes and/or hydrazones) might be used in place of the enamides. Preliminary experiments[6] with oximes (such as **3a**) afforded only evidence of simple debromination (*i.e.* **3b**). As previously noted,[4,5] facile cyclization appears to require a large substituent (*i.e.* R_2 on **1**) on the nitrogen adjacent to the carbonyl.



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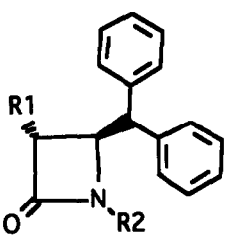

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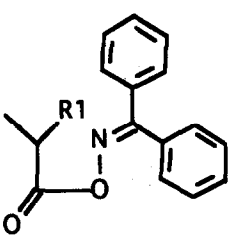


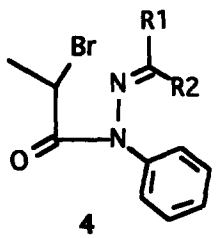
3

a R_1= CH_3, R_2= C_6H_{11}
b R_1= CH_3CH_2, R_2= C_6H_{11}
c R_1= CH_3, R_2 = *tert*-C_4H_9
d R_1 = CH_3CH_2, R_2 = *tert*-C_4H_9

a R_1=Br
b R_1=H

An interesting and unexpected reaction pathway has now been observed for a selected series of α-bromoacylated phenylhydrazones (*e.g.* **4a,..,4g**). These substrates were prepared by hydrazone formation (using a simple Dean-Stark procedure for most examples) from the appropriate carbonyl compound followed by reaction with the requisite α-bromo acid halide and a final careful chromatography.[7]

Slow steady addition via a syringe pump of a benzene solution of AIBN and tributyltin hydride to a refluxing benzene solution of hydrazone **4a** gave, after routine purification (*e.g.* via flash column or radial chromatography), an initially mysterious product. Although the spectroscopic data were not compatible with the expected formation of a four-membered heterocycle, the infrared, proton nmr, carbon nmr, and mass spectroscopy did indicate the presence of an amide-like moiety.[8] The high crystallinity of the unknown reaction product permitted a single-crystal x-ray study[9] that unambiguously established the structure as a 2-phenylpyrazolidin-3-one derivative **5a**. This reaction was found to be quite general and to proceed in moderate to high yields especially when one or more of the substituents R_1 or R_2 is aryl. Spirocyclic sytems (*e.g.* **5c** and **5g**) are easily obtained by radical cyclization of the corresponding acylated hydrazones that, in turn, are derived from cyclic ketones (*e.g.* 9-fluorenone and cyclohexanone, respectively). Enhanced formation of the main by-product, the corresponding debrominated acylated hydrazone **6**, becomes more significant as more aliphatic substituents are present on the hydrazone (**Table 1**). Brominated substrates whose hydrazones are derived from aliphatic ketones undergo cyclization in, at best, only moderate yield.



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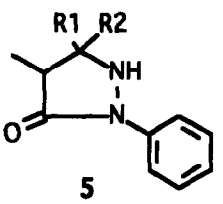

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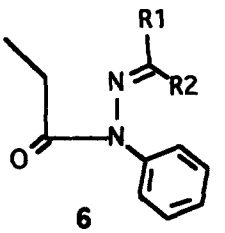


6

For structures **4**, **5**, and **6**, R_1 and R_2 as in **Table 1**.

Table 1:

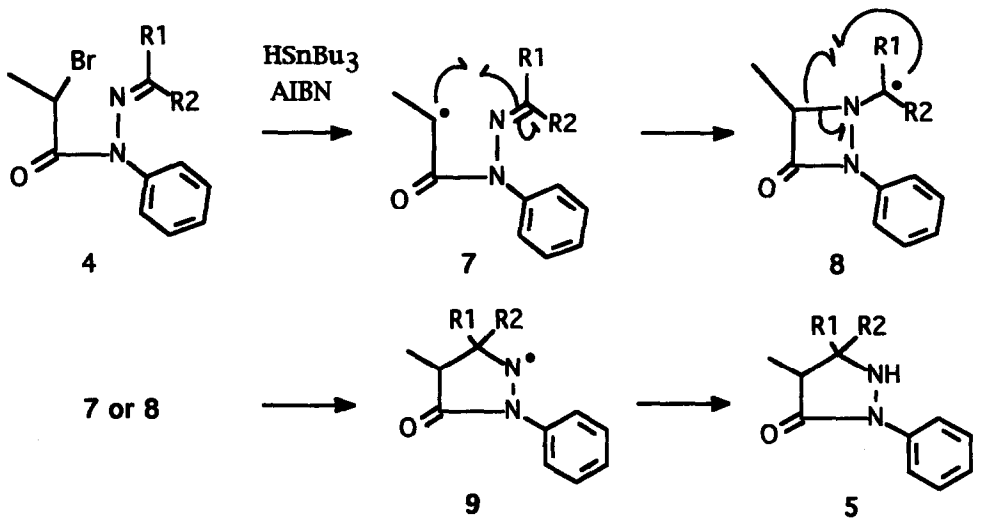
Substrate	R_1	R_2	5:6	5 (%)	6 (%)
4a	Ph	Ph	1:0	92	~0
4b	Ph-p-OMe	Ph-p-OMe	1:0	90	~0
4c	R1, R2 = 9-fluorenyl	_	1:0	89	~0
4d	Ph	CH_3	1:0	73	~0
4e	Ph	H	2:1	65	30
4f	$PhCH_2$	$PhCH_2$	1:1.3	32	43
4g	R1, R2 = $(CH_2)_5$	_	2:1	35	18

For the benzaldehyde hydrazone based substrate **4e**, only one diastereoisomer

could be detected by TLC and proton nmr. A single-crystal x-ray study[10] performed on **5e** established the relative configuration as trans for the substituents at C-2 (*e.g.* the Me group) and C-3 (*e.g.* the phenyl ring). A typical experimental procedure (leading to **5e**) and representative spectral data are appended.[11]

One of several possible mechanisms for heterocycle formation is shown below. By analogy to the intermediates proposed for beta-lactam formation from α-brominated enamides,[5] the initially formed radical **7** could undergo cyclization to the 4-exo product **8**. Rapid transformation of **8** into the ring-expanded N-stabilized radical **9** could then be followed by hydrogen atom transfer from the tributyltin hydride to continue the chain. However, **9** could also be formed directly from **7**. An alternative thermal electrocyclic mechanism involving hydrazone **4** is unlikely since prolonged reflux of hydrazone **4** in benzene in the absence of both AIBN and tributyltin hydride fails to afford a detectable trace of **5**.

Scheme 1



The 2-phenylpyrazolidin-3-one compound class has been found[12] to undergo facile photo-isomerization to 1-amino-substituted-β-lactams. Thus, this new methodology, in principle, provides a convenient synthetic bridge from readily available ketone/aldehyde and carboxylic acid precursors to a structurally diverse group of monocyclic β-lactam derivatives.[13]

Acknowledgements

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7. All reported compounds were chromatographically homogeneous and were characterized by IR, ^{1}H NMR, ^{13}C NMR, low res. m/z and high res. m/z. Photocopies of spectroscopic and crystallographic data supplied on request. Several hydrazone and acylated hydrazone intermediates give evidence of the presence of cis/trans isomers.
8. Especially the strong IR band at 1698.4 cm^{-1}.
9. Ho, D. M.; University of Cincinnati, unpublished results, 1991. Final R(F) = 0.0530 and wR(F) = 0.0602.
10. Krause, J.; University of Cincinnati, unpublished results, 1992. Final R(F) = 0.0671 and wR(F) = 0.0827.
11. **Hydrazone:** Combine benzaldehyde (5.306 g (0.050 moles)), phenylhydrazine (4.90 mL (0.050 moles)), pyridine (4.1 mL (0.050 moles), conc. HCl (4.2 mL), and EtOH (150 mL), heat to reflux for 3 h, cool in ice-bath, filter off crystals, wash with cold EtOH, air-dry (mp 110-113°C), and use immediately. **Acylated Hydrazone 4e:** To an oven-dried apparatus was added CH_2Cl_2 (40 mL), pyridine (0.89 mL), and hydrazone (1.96 g (10.0 mmoles)). The resulting solution was cooled to 0°C. A soln. of α-bromopropionyl bromide (1.15 mL (11.0 mmoles)) in 15 mL of CH_2Cl_2 was added dropwise. After stirring for several hrs. the reaction mixture was washed twice with water, dried, and the volatiles removed. Radial chromatography (4 mm SiO_2 plate: gradient - (0% EtOAc/100% ligroin) to (15% EtOAc/85% ligroin)) gave off-white solid that was used as is (2.56 g (77%)). Partial ^{1}H NMR (250 MHz) δ 1.96 (d, 3H, J = 7.1 Hz), 5.74 (q, 1H, J = 7.1 Hz). **2-Phenylpyrazolidin-3-one 5e:** To oven-dried apparatus consisting of RBRF, magnetic stirrer, reflux condenser, and N_2 inlet was added benzene (ca. 60 mL) and **4e** (0.662 g (2.00 mmoles)). The resulting solution was brought to gentle reflux and a solution of AIBN (40 mg), tributyltin hydride (1.20 g (2.40 mmoles)), and benzene (ca. 10 mL) was added over 10 hrs. followed by gentle reflux for a further 6 hrs. The volatiles were removed, the reaction mixture was diluted with CH_3CN (130 mL), and washed 5x20 mL with ligroin. Careful flash chromatography (50 g silica: gradient - (0% EtOAc/100% ligroin) to (7% EtOAc/92% ligroin)), using 500 mg out of crude reaction mixture (0.668 g total (over theory)), gave a purified yield of (0.245 g (65% based on total crude recovered). of **5e** plus (0.115 g (30% based on total crude recovered)) of reduction product **6e**. For **5e**: IR: carbonyl band at 1697.5 cm-1; Partial ^{1}H NMR δ 1.30 (d, 3H, J = 6.5Hz), 4.28 ("t" (overlapping dd), 1H, J~11Hz), 4.53 (d, 1H, J = 11.2 Hz); high res. M+ cal'd 252.1263/found 252.1252.
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