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Tetrahedron Letters 45 (2004) 4441–4444
Tetrahedron Letters

New regio and stereoselective intermolecular Pauson–Khand reactions of allenamides

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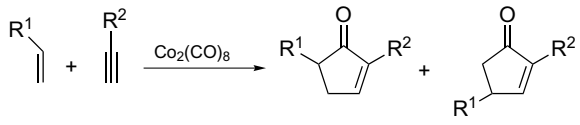
Received 29 March 2004; revised 13 April 2004; accepted 13 April 2004

Abstract—Intermolecular Pauson–Khand reactions are still quite limited in scope and yields. There are also few reports using allenes as the olefinic part in this version. We report herein new regio and stereoselective reactions of allenamides with several alkynes. These reactions give functionalized cyclopentenones bearing an exocyclic enamide, which can be useful synthetic intermediates.

Allenamines and allenamides are an emerging group of substrates that are becoming useful in organic synthesis.[1] Although there are still very few literature examples using allenamines, this electron enriched allenes have found use in some reactions with electrophiles and in certain cyclizations. The parent allenamides are more stable and thus are increasing their use in synthetic methodologies.[2]

On the other hand, the Pauson–Khand reaction (PKR) is a powerful tool in the synthesis of cyclopentenones, a structural feature present in a large variety of natural products.[3] The intermolecular version of this reaction is still quite limited, as unstrained olefins scarcely react.[4] Some vinylethers/esters[5] and vinyl sulfoxides[6] are also useful in the intermolecular PKR. The use of traceless tethers[7] or directing groups like pyridisilyl[8] are strategies that circumvent partially this problem, also avoiding the formation of regioisomeric mixtures. In the majority of cases, the intermolecular PKR is regioselective from the alkyne being the bulkier substituent situated adjacent to the carbonyl in the final product. It has been demonstrated recently that both steric and electronic effects may be responsible for this regioselectivity.[9] Unsymmetrical olefins usually give mixtures of regioisomers (Scheme 1).



Scheme 1.

There are a wide variety of catalytic protocols available to effect this reaction, some of them under mild conditions. Nevertheless the catalytic PKR is not a completely solved problem specially in the intermolecular processes where there are still few results.[3b]

Allenes are one of the most promising substrates for the PKR introduced in the past years. Several groups have used the intramolecular allenic PKR for the synthesis of medium sized rings. However there is only one precedent in the use of simple allenes in an intermolecular PKR due to Cazes and co-workers.[10] There is also a precedent of an intramolecular PKR with an allenamide equivalent.[11]

We herein report new intermolecular PKR of allenamides. These reactions show many possibilities in selectivity, and as we will see have resulted to be very regio and stereoselective.

To explore this chemistry we carried out the synthesis of a series of allenamides bearing aromatic rings. This synthesis was effected using a classical strategy depicted

Keywords: Intermolecular Pauson–Khand; Allenamides; Cobalt.
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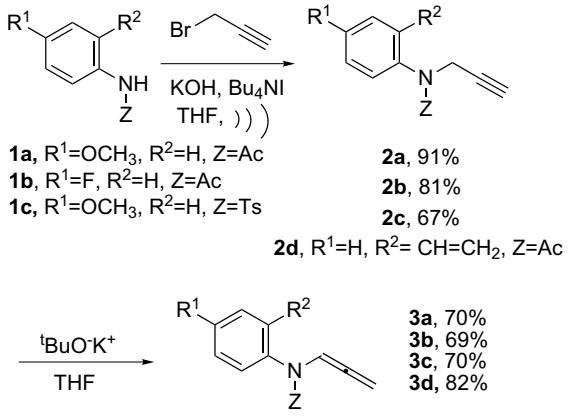
doi:10.1016/j.tetlet.2004.04.061



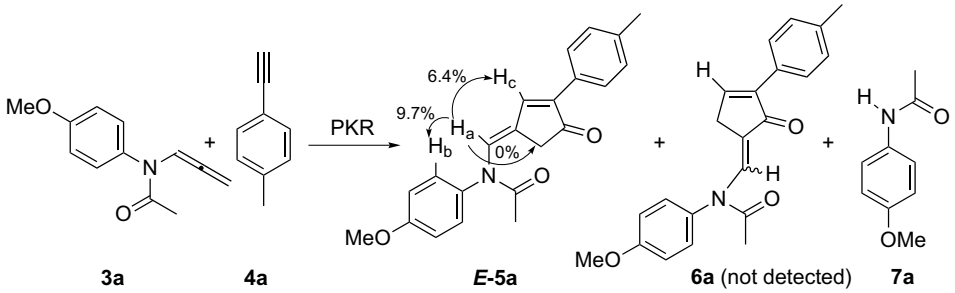
Scheme 2.

in Scheme 2. Starting from tosylanilides and acetanilides **1**, propargylation under sonication using solid KOH as the base gave the corresponding propargylamides **2** in good yields. These compounds were converted totally into the corresponding allenamides **3** by treatment with ^{t}BuOK. In the synthesis of **3c** some amount of allene is formed in the propargylation reaction but we were unable to have good direct conversions from **1** into **3** that would improve the two-step process.[12] One of the allenes formed, compound **3d**, was designed to show the competence in the PKR of the allene and the olefin. We obtained this substrate from our previously described product **2d**.[13]

The Pauson–Khand reaction of compound **3a** with *p*-tolylacetylene, **4a**, was selected as a model to test several conditions. We used first two reaction conditions developed in our group that use molecular sieves as promoters. However, in this case, we found no results probably due to decomposition of the allenamide. Molecular sieves are known for being catalysts in the formation of enamines and thus it is possible that they would accelerate the decomposition of our starting materials.[14] Thus, we used trimethylamine *N*-oxide (TMANO) and *N*-methylmorpholine *N*-oxide (NMO) as promoters testing several solvents. Heat promotion was also unsuccessful due to thermal decomposition of the allenamide. The results are summarized in Table 1. Entries 1–3 show that the presence of molecular sieves and/or heat prevent the formation of the PK product probably due to rapid decomposition of the allene into the acetanilide **7a**, which was isolated in high yield.

Among the conditions tested, those of entry 6, were selected. Although yields were still not excellent in this example, the reaction gave only one compound, jointly with a small amount of a mixture of other compounds, which could not be identified and with a 7% of **7a**. The structure of the major reaction product was assigned based on NMR experiments as *E*-**5a**. The first important data is the position of the signal of the CH_2 of the cyclopentenone. This carbon appears at 38 ppm, which agrees with calculated values for compound **5a**. The CH_2 in **6a** is expected to appear at 22 ppm. Additionally, NOE experiments showed that irradiation of H_a lead to a 9.7% increment in the signal of H_b and a 6.4% increment in H_c. No effect was observed in the signal corresponding to the CH_2. These increments demonstrate an *E*-stereochemistry for the reaction product. It is interesting to note the great number of possibilities in the formation of isomers that are possible in this reaction. The regioselectivity from the alkyne part follows the vast number of examples reported in the literature and the bulky substituent is placed near the carbonyl. On the other hand it is rare to find intermolecular PKR with nonsymmetric olefins that do not give mixtures of regioisomers. In our case we only detected the product with the exocyclic double bond in the β-position. This exocyclic double bond has two possible stereochemistries, being the *E*-compound the only one isolated. When purifying the crude mixture, small amounts of complex mixtures were separated from *E*-**5a**, being the only other

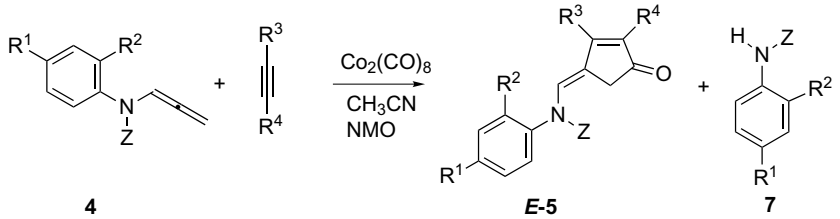
Table 1. Reaction conditions for the PKR of compound **4a**



Entry	Solvent	Conditions	Yield of **7a** (%)[a]	Yield of *E*-**5a** (%)[a]
1	Toluene	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, 4 Å mol. sieves, reflux	75	<5
2	Toluene	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, 4 Å mol. sieves, 9 equiv TMANO, rt	28	10
3	Toluene	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, reflux	80	<5
4	Toluene	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, 9 equiv TMANO, rt	18	18
5	CH_3CN	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, 9 equiv TMANO, rt	8	32
6	CH_3CN	1.5 equiv alkyne, 1.5 equiv $Co_2(CO)_8$, 6 equiv NMO, rt	7	45

[a] In pure product with correct spectroscopical and analytical data.

Table 2. Intermolecular PKR of alleneamides



4 ***E*-5** **7**

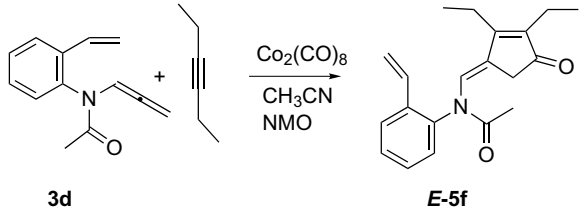
Entry	Substrate	R^1	R^2	*Z*	R^3	R^4	Product	Yield of **7** (%)[a]	Yield of *E*-**5** (%)[a]
1	**3a**	MeO	H	Ac	*p*-Tolyl	H	*E*-**5a**	7	45
2	**3a**	MeO	H	Ac	Bu	H	*E*-**5b**	8	50
3	**3a**	MeO	H	Ac	Et	Et	*E*-**5c**	10	65
4	**3b**	F	H	Ac	Et	Et	*E*-**5d**	9	61
5	**3c**	MeO	H	Ts	Et	Et	*E*-**5e**	5	85
6	**3d**	H	$CH{=}CH_2$	Ac	Et	Et	*E*-**5f**	—	58
7	**3c**	MeO	H	Ts	*p*-Tolyl	H	*E*-**5g**	—	25
8	**3c**	MeO	H	Ts	CH_2OH	H	—	—	—
9	**3c**	MeO	H	Ts	Pr	TMS	*E*-**8h**+*E*-**5h** (4:1)	—	85[b]
10	**3c**	MeO	H	Ts	$CH_2OTBDMS$	TMS	*E*-**8i**+*E*-**5i** (4:1)	—	78[b]

[a] In pure product with correct analytical and spectroscopic data.
[b] In pure mixture of both isomers.

compound that could be identified in those mixtures, one isomer of *E*-**5a** that we have assigned to *Z*-**5a**.

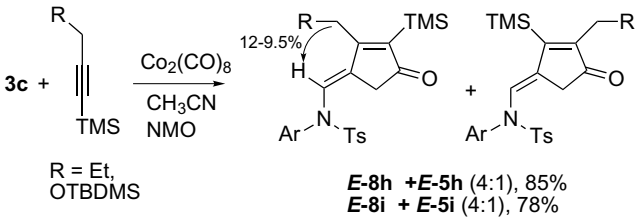
Substrate scope for this process was then addressed. The results are summarized in Table 2.[15] Yields are moderate with terminal alkynes (entries 1,2) even when switching the allenamide protecting group to tosyl (entry 7). We also noted an unsuccessful result with propargyl alcohol (entry 8). On the other hand, nonterminal alkynes gave better results (entries 3–6) and we recorded some excellent yields. Reaction of entry 6 was performed to study the competence between the olefin and the allene. We did not observe any reaction with the olefin, being *E*-**5f** the only observed product (Scheme 3). The NOE experiments effected in all the products showed they all had the same *E*-stereochemistry. The reactions of entries 2 and 7 were sluggish and other isomers might have been present in the crude mixtures.

In view of these results we carried out the reaction of **3c** with 1-trimethylsilyl-1-pentyne (entry 9). This reaction led to a 4:1 mixture of isomers in 85% yield. The reaction with protected propargyl alcohol (entry 10) led smoothly and with good yield to 4:1 mixture of isomers. These two isomers are the regioisomers derived from the two possible orientations of the alkyne. A small amount of the major isomer was separated for characterization (Scheme 4).



3d ***E*-5f**

Scheme 3.



Scheme 4.

The NOE experiments showed the major compounds corresponded with *E*-**8h–i** with the TMS group in the α-position, being *E*-**5h–i** the minors.

In conclusion we have described a highly selective intermolecular PKR of allenamides that give interesting funtionalized cyclopentenones, which we will use as synthetic intermediates in the synthesis of natural products. We are currently completing the study on the scope of this reactions and on the chemistry of these new products.

Acknowledgements

This work was supported by MCYT-Spain, BQU2002-00137) and the Universidad San Pablo-CEU (grant 07/03). A.P. acknowledges fellowship from the FUSP-CEU.

References and notes

1. Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773–782.
2. For recent references see: (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136; (b)

Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694–12695.
3. Recent reviews on the Pauson–Khand reaction: (a) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32–42; (b) Gibson, S. E.; Stevenazzi, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810; (c) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589–1595; (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3282; (e) Keun Chung, K. *Coord. Chem. Rev.* **1999**, *188*, 297–341.
4. A recent DFT study rationalizes the reactivity of different olefines: de Bruin, T. J. M.; Milet, A.; Greene, A. E.; Gimbert, Y. *J. Org. Chem.* **2004**, *69*, 1075–1080.
5. Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104–117.
6. Rodriguez-Rivero, M.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992–14993.
7. Reichwein, J. F.; Iacono, S. T.; Pagenkopf, B. L. *Tetrahedron* **2002**, *58*, 3813.
8. Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3481.
9. Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 5396–5400.
10. Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 4417–4420.
11. Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869–2871.
12. This behavior of tosylamides has been described earlier: van Boxtel, L. J.; Körbe, S.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 2283–2292.
13. Domínguez, G.; Casarrubios, L.; Rodriguez-Noriega, J.; Pérez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856–2861.
14. Pérez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2000**, *65*, 3513–3519, and references cited therein.
15. Typical experimental procedure for the synthesis of *E*-**5e**: To a solution of 3-hexine (135 μL, 1.19 mmol) in acetonitrile (8 mL), $Co_2(CO)_8$ (407 mg, 1.19 mmol) was added and the resulting mixture was stirred for 90 min at room temperature. The solution was then cooled in an ice/water bath and NMO (557 mg, 4.76 mmol) was added. A solution of allene **3a** (250 mg, 0.79 mmol) in acetonitrile (8 mL) was then added to the reaction mixture and this was stirred at room temperature overnight. The reaction mixture was filtered off through a celite pad and washed with acetonitrile (10 mL). The solvent was removed and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) affording 288 mg (85%) of the product *E*-**5e** as a white solid. Mp 122–24 °C Et_2O). ^1H NMR ($CDCl_3$): 0.91 (t, 3H, CH_3, $J = 7.7$ Hz), 1.18 (t, 3H, CH_3, $J = 7.7$ Hz), 1.96 (s, 2H, CH_2), 2.14 (q, 2H, CH_2, $J = 7.7$ Hz), 2.38 (s, 3H, CH_3), 2.53 (q, 2H, CH_2, $J = 7.7$ Hz), 3.75 (s, 3H, CH_3), 6.75 (d, 2H, Ar, $J = 9.3$ Hz), 6.85 (d, 2H, Ar, $J = 8.8$ Hz), 7.16 (s, 1H, CH), 7.24 (d, 2H, Ar, $J = 8.2$ Hz), 7.50 (d, 2H, Ar, $J = 8.2$ Hz). ^{13}C NMR ($CDCl_3$): 204.2, 169.0, 159.8, 144.3, 140.4, 134.7, 131.2, 129.6, 129.2, 127.4, 122.1, 119.1, 114.3, 55.2, 37.0, 21.4, 19.3, 16.3, 13.8, 13.2. IR (KBr): 1690 (C═O), 1350 (SO_2), 1180 (SO_2). Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.74; H, 6.40; N, 3.29; S, 7.54. Found: C, 67.87; H, 6.48; N, 3.41; S, 7.32.