Tetrahedron Letters 54 (2013) 3101–3104

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel supported and unsupported prolinamides as organocatalysts for enantioselective cyclization of triketones

Rafael Pedrosa *, José María Andrés *, Rubén Manzano, César Pérez-López

Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Paseo de Belén 7, 47011 Valladolid, Spain

ARTICLE INFO

Article history:
Received 18 February 2013
Revised 26 March 2013
Accepted 29 March 2013
Available online 9 April 2013

Keywords:
Aldol reaction
Enantioselective synthesis
Organocatalysis
Prolinamides
Supported prolinamides

ABSTRACT

A novel prolylsulfonamide derived from ethylene diamine and its supported counterpart has been prepared and tested as enantioselective intramolecular aldol reaction of cyclic and acyclic triketones. Good to excellent yields and enantioselectivities have been obtained in water and under solvent free conditions.

Intramolecular enantioselective aldol condensation is a very interesting reaction because it allows the construction of cyclic ketones present in a lot of natural products and building blocks. Special interest was shown tothe organocatalytic enantioselective synthesis of both Wieland–Miescher (WMK) (**1**) and Hajos–Parrish (HPK) (**2**) ketones starting from 2-substituted 1,3-cyclohexanedione or 1,3-cyclopentanedione, respectively[1] (Fig. 1). A lot of catalysts have been tested for that enantioselective cyclization, including amines,[2] peptides,[3] α-amino acids,[4] β-amino acids,[5] and proline derivatives,[6] but the most commonly used are prolinamides. Although prolinamide itself works well as organocatalyst in that reaction,[7a] substituents at the nitrogen atom such as phenyl,[7a] 3,5-bis(trifluoromethyl) phenyl,[8] *p*-toluene sulfonyl,[7] Binam,[9] or prolinethioamides derived from amino indane[10] improve both the reactivity and the enantioselectivity.

Specially important is the search for novel insoluble supported catalysts because of the easy separation from the reaction mixture and their re-use,[11] but all the immobilized organocatalysts described until now did not work in the intramolecular aldol reaction,[12] or yielded the condensation products in moderate enantioselectivity.[13] Based on our previous results on enantioselective aldol reactions,[14] we report now on a short synthesis of a novel prolylsulfonamide, and its immobilized counterpart, starting from cheap and easily available materials. The ability of these novel catalysts to promote enantioselective transformations has been tested on the cyclization of open-chain triketones and the synthesis of Wieland–Miescher (**1**) and Hajos–Parrish (**2**) ketones.

The synthesis of the catalysts is summarized in Scheme 1. Prolylsulfonamide **4** was prepared by reaction of the known monotosylated ethylenediamine **3**[15] with Boc-(L)-proline and subsequent deprotection with trifluoroacetic acid. The supported prolinamide **6** was synthesized in two different ways from 1,2-ethylenediamine. The reaction of the diamine with the commercially available chlorosulfonyl polystyrene PS-1% DVB (100–200 mesh) as previously described[16] led to **5**, which was coupled with Boc-(L)-proline and deprotected by treatment with TFA in methylene chloride. Alternatively, **6** and *ent*-**6** were obtained by condensation of 1,2-ethylenediamine with Boc-(L)- or Boc-(D)-proline to **7** or *ent*-**7**, respectively, followed by reaction with the chlorosulfonyl polystyrene and deprotection.

The microanalysis of the N and S-atoms showed 66% (f = 1.45 mmol g^{-1}) incorporation of prolinamides to the polymer in the first method and 97% (f = 1.68 mmol g^{-1}) in the second one.

The catalysts **6** and *ent*-**6** prepared in the second way and, for comparative purposes, prolinamide **4** were used to establish the

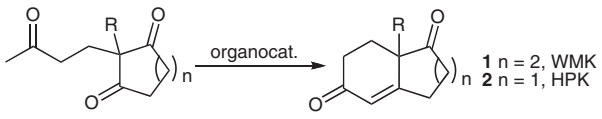

Figure 1.

* Corresponding authors.
E-mail address: pedrosa@qo.uva.es (R. Pedrosa).

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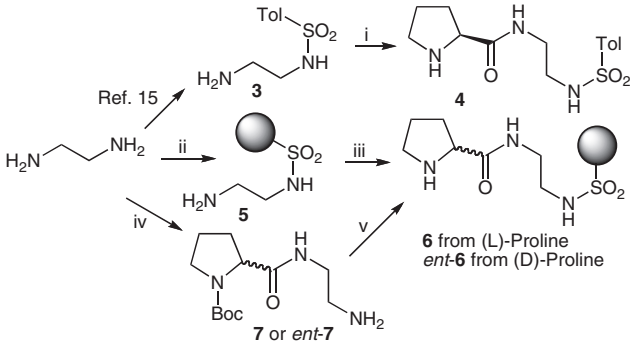
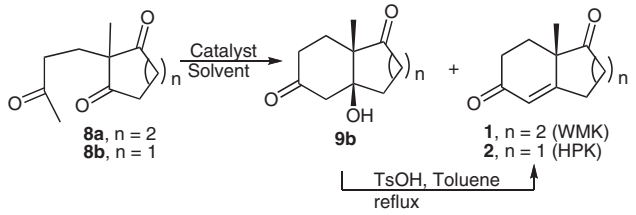
http://dx.doi.org/10.1016/j.tetlet.2013.03.123



Scheme 1. Reagents and conditions: (i) 1. Boc-(L)-proline, DCC, DCM, 0 °C to rt (97%). 2. TFA, DCM, rt (80%). (ii) Chlorosulfonylated polystyrene (PS-1% DVB), EDA, DME, 0 °C to rt. (iii) 1. Boc-(L)-proline, DIC, DCM, 0 °C to rt. 2. TFA, DCM, rt, 6 h. (iv) Boc-(L)-proline, or Boc-(D)-proline, ClCO2Et, NMM, DCM, 0 °C, 30 min., then ethylene diamine, DCM, −78 °C to rt (77%). (v) 1. Chlorosulfonylated polystyrene (PS-1% DVB), DCM, Et_3N, rt, 4 days. 2. TFA, DCM, rt, 6 h.



Scheme 2. Organocatalytic enantioselective synthesis of Wieland–Miescher and Hajos–Parrish ketones.

best reaction conditions in the enantioselective synthesis of WMK (**1**) and HPK (**2**) (Scheme 2 and Table 1).

We first tested the cyclization of 1,3-cyclohexanedione derivative **8a** to the Wieland–Miescher ketone **1** with prolylsulfonamide **4** and *p*-nitrobenzoic acid as co-catalyst in different solvents and conditions. At 20 °C, in acetonitrile, the aldol-dehydration process finished in 48 h, yielding (*S*)-**1** in excellent yield and enantioselectivity (entry 1 in Table 1). This result is comparable to those obtained with prolinamide derived from 3,5-bis(trifluoromethyl)aniline[8] or proline itself.[2a,b] When the reaction temperature was lowering to −18 °C the reaction time increased to 96 h, and the enantiomeric ratio (er) slightly increased to 97:3, but the yield decreased to 80% (entry 2). In the same reaction conditions the reaction also worked well in chloroform and toluene, leading to WMK (**1**) in excellent yields and enantioselectivities (entries 3 and 4 in Table 1). A quite different behavior was observed in the reactions promoted by the supported catalyst. Acetonitrile is not a good solvent for that reaction because it was necessary to increase the reaction time to 3 weeks to obtain 70% of (*S*)-**1** in 86:14 er when the supported prolinamide **6** (20 mol %) and acetic acid (20 mol %) were used as catalysts (entry 5). On the contrary, the reaction was accelerated in water leading to the cyclization product in 75% yield and 83:17 er by stirring for 48 h at 20 °C with 10 mol % of **6** and 10 mol % of AcOH as co-catalyst (entry 6). A slight increase in the enantioselection, but a decrease in the yield was observed when the reaction was carried out at 0 °C, although at the expense of increasing the reaction time to 120 h (entry 7). As expected, the enantiomeric (*R*)-Wieland–Miescher ketone (*ent*-**1**) was formed when the supported catalyst *ent*-**6**, derived from (D)-proline, was used as promoter of the reaction (entry 8 in Table 1).

Fortunately, the best results in terms of yield and enantioselectivity for the synthesis of (*S*)-**1** were obtained in neat conditions. In fact, (*S*)-**1** was isolated in 80% yield and 89:11 er (entry 9) when a neat mixture of **8a**, 10 mol % of catalyst **6** and 10 mol % of AcOH as co-catalyst was stirred at 20 °C for 24 h, but the reaction failed when the co-catalysts were changed to PNBA (entry 10 in Table 1), probably because of the insolubility of the acid in the reaction mixture. Excellent yield (83%) and enantioselection (er 95:5) were also obtained when the reaction was promoted by unsupported catalyst **4** under neat conditions (entry 11 in Table 1). To the best of our knowledge, this is the best result obtained until now in the enantioselective synthesis of **1** by using a supported organocatalyst.[17]

1,3-Cyclopentane dione derivative **8b** was cyclized to Hajos–Wiechert ketone (*S*)-**2** in excellent yield and enantioselectivity in the reaction was promoted by 20 mol % of prolylsulfonamide **4** in acetonitrile at −18 °C (entry 12 in Table 1), but the dehydration process occurred very slowly in the reaction promoted by the supported prolinamide **6** in water. In that solvent, the cyclization

Table 1
Enantioselective cyclizations of triketones **8a**,**b** to WMK (**1**) and HPK (**2**)

Entry	Ketone/catalyst (%)	Solvent	T (°C)	Time (h)	Products (yield)[a]	er[b]
1[c]	**8a**/**4** (20)	MeCN	20	48	**1** (85)	96:4
2[c]	**8a**/**4** (30)	MeCN	−18	96	**1** (80)	97:3
3[c]	**8a**/**4** (20)	$CHCl_3$	−18	96	**1** (92)	93:7
4[c]	**8a**/**4** (20)	Toluene	−18	120	**1** (95)	92:8
5[d]	**8a**/**6** (20)	MeCN	20	504	**1** (70)[e]	86:14
6[d]	**8a**/**6** (10)	H_2O	20	48	**1** (75)	83:17
7[d]	**8a**/**6** (10)	H_2O	0	120	**1** (65)	85:15
8[d]	**8a**/ *Ent*-**6** (10)	H_2O	0	120	**1** (64)	16:84
9[d]	**8a**/**6** (10)	neat	20	24	**1** (80)	89:11
10[c]	**8a**/**6** (10)	Neat	20	24	—	—
	8a/**4** (10)	neat	20	24	**1** (83)	95:5
10[c]	**8b**/**4** (10)	MeCN	−18	96	**2** (95)	92:8
11[d]	**8b**/**6** (10)	H_2O	20	48	**9b** (88)[e] **2** (12)[e]	nd
12[d]	**8b**/**6** (10)	H_2O	20	96	**9b** (53)[e] **2** (47)[e]	nd
13[d]	**8b**/**6** (10)	H_2O	20	168	**2** (52)[f]	80:20
14[d]	**8b**/**6** (20)	H_2O	0	96	**2** (43)[f]	78:22
15[d]	**8b**/**6** (10)	neat	20	72	**2** (70)	88:12[g]

[a] Yields determined after chromatographic purification.
[b] Enantiomeric ratio determined by chiral HPLC.
[c] BA as co-catalyst.
[d] HOAc as co-catalyst.
[e] Ratio determined by ^{1}HNMR of the reaction mixture.
[f] After dehydration of the mixture of **9b** and **2** with pTsOH in toluene at reflux.
[g] 78:22 is the best er reported by using a supported catalyst (Ref. 13b).