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Stereoselectivity in the Wittig Reaction of Phenyl 3-Pyridyl Ketones: Amide Substituent Effect on the Preferential (*E*)-Olefin Formation

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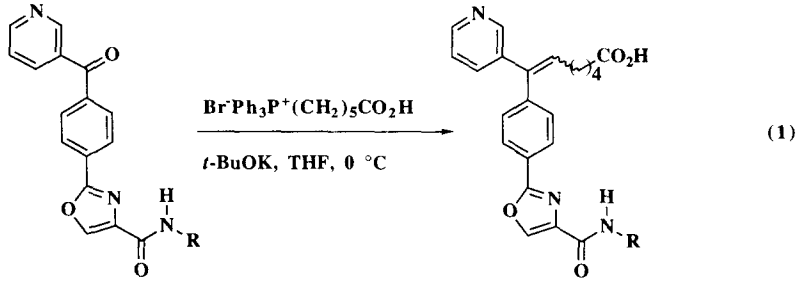
Abstract: A Wittig reaction of amide substituted phenyl 3-pyridyl ketones with "nonstabilized" phosphorus ylides which contain a carboxyl terminus preferentially forms (*E*)-olefin. The preference for this stereoselectivity stems from either hydrogen bonding or salt-bridge formation between the amide group and the carboxyl terminus during the oxaphosphetane intermediate formation.

An unusual (*E*)-stereoselective Wittig reaction of "nonstabilized" phosphorus ylides bearing anionic substituents with aromatic aldehydes has been reported.[1-3] We have reported[4,5] that a Wittig reaction of sulfonamido-substituted phenyl 3-pyridyl ketones with phosphorus ylides which contain a carboxyl terminus results in high (*E*)-olefin formation. In our report[5] we verified experimentally and computationally that hydrogen bonding or salt-bridge formation between the sulfonamido group and the carboxyl terminus during formation of the oxaphosphetane intermediate dictated the stereochemical outcome.

In this paper we report a similar observation of preferential (*E*)-olefin formation in the Wittig reaction of phenyl 3-pyridyl ketones bearing an oxazole carboxamide with (5-carboxypentylidene)triphenylphosphorane (**1**: $Ph_3P{=}CH(CH_2)_4COO^-K^+$) (eq 1):



(1)

We speculated that the (*E*)-stereoselectivity in this reaction was effected by the amide substituent rather than the oxazole ring, as noted for the sulfonamido-substituted phenyl 3-pyridyl ketones. The following findings support this hypothesis. N-cyclohexylbutyl substituted oxazole carboxamide derivatives produced (*E*)-olefins, even when the alkyl chain length of (ω-carboxyalkyl)triphenylphosphonium bromide was shortened (entries **2a**, **b**, and **c**, Table 1). The longer chain phosphonium salt resulted in better (*E*)-selectivity than the shorter chain phosphonium salt possibly due to the enthalpic advantage for a larger macrocycle formation via a hydrogen bond or salt-bridge.[5] An oxazoline derivative **3** also preferentially formed an (*E*)-olefin.[6]

As already seen,[4,5] sulfonamido-substituted derivatives preferred (*E*)-olefin formation (entries **4** and **5**). The better selectivity in **5** may be attributed to the flexibility of the (sulfonylamino)methyl group which can

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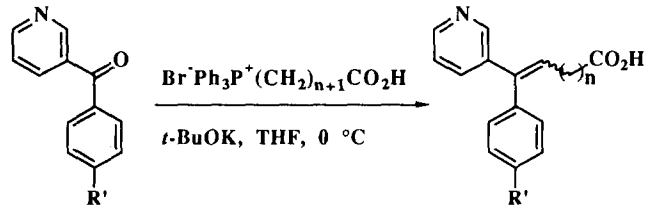
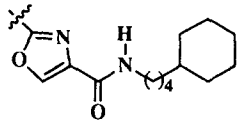
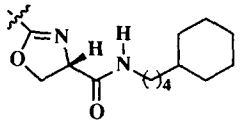
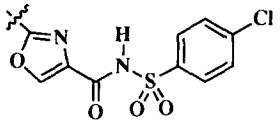
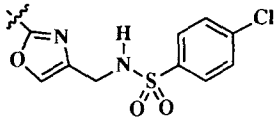
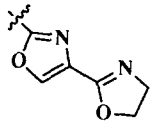
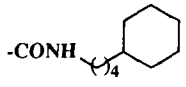
Table 1. Stereoselectivity of Wittig Reaction:



Entry	R'	n	Yields (%)[a]	E : Z[b]
2a		2	53	6.2 : 1
b		4	90	8.7 : 1
c		5	76	10.6 : 1
3a		4	39	10 : 1
b			37	8 : 1[c]
4		4	38	6 : 1
5		4	100	9.6 : 1
6	-N(Me)SO₂Ph	4	80	1 : 2.8
7		4	29	1 : 2.8
8a		4	63[d]	9.5 : 1[d]
b			94	1 : 1.3[e]
9	-CONMe₂	4	39	1.3 : 1
10	-NHCOCH₃	4	91	33 : 1

[a]Isolated yields. The reactions have not been optimized. [b]The ratio was determined either by ^{1}H NMR or HPLC analysis. [c]See note 6. [d]Determined as methyl ester. [e]$BrPh_3P(CH_2)_5CH_3$ was used instead of $BrPh_3P(CH_2)_5CO_2H$.

interact better with the carboxyl terminus of the phosphonium salt as compared to that of sulfonyl-substituted amide in **4**. Previously we reported that a sulfonamide without a NH proton (entry **6**) reversed the preference of olefin geometry to a (*Z*)-isomer.[5]

In contrast, a ketone which does not bear an amide functionality (entry **7**) resulted in preferential (*Z*)-olefin formation, albeit in modest selectivity, just as we have observed in the Wittig reaction of phenyl 3-pyridyl ketones bearing other substituents rather than sulfonamide group.[5]

In order to confirm that the amide, but not the oxazole ring, is dictating this stereochemical outcome, we further investigated a Wittig reaction with a ketone which was not substituted with an oxazole. [(N-cyclohexylbutyl)amino]carbonyl substituted ketone[7] yielded alkenoic acids **8a** in an *E*:*Z* ratio of 9.5:1.[8] An inverse amide substituted ketone[9] should also give rise to (*E*)-preference if this hydrogen bond/salt-bridge hypothesis were operating in the reaction mechanism of these Wittig reactions. The entry **10** substantiated this assumption. This hypothesis was further supported by the results when one of the two hydrogen bonding groups, the carboxyl or the NH proton, was removed from the substrates. When [(N-cyclohexylbutyl)amino]-carbonyl substituted ketone[7] was reacted with hexyltriphenylphosphonium bromide, the (*Z*)-olefin was preferentially formed (entry **8b**). Dimethylaminocarbonylphenyl ketone when reacted with (5-carboxy-pentyl)triphenylphosphonium bromide lost stereoselectivity in the olefin geometry (entry **9**).

The following is a typical example of the Wittig reaction: To a mixture of 142.2 mg (0.59 mmol) of 4-acetamidophenyl 3-pyridyl ketone and 2 equiv (541.4 mg) of (5-carboxypentyl)triphenylphosphonium bromide in 3.5 mL of freshly distilled THF was added dropwise 4 equiv (2.4 mL) of 1.0 M *t*-BuOK in THF at 0 °C under N_2 atmosphere. The orange colored solution was stirred at 0 °C for 4 hr (the reaction was monitored by TLC to completion). The reaction was quenched with ca. 0.45 mL of 5 N HCl, adjusting pH to ~6. The mixture was then concentrated and purified by flash chromatography with 7 : 1 : 92 MeOH-HOAc-CH_2Cl_2 as eluent to yield 182.9 mg (91%) of the (*E*/*Z*) mixture of alkenoic acids **10** (*E*:*Z* = 33:1).[10]

In conclusion, a Wittig reaction of amide substituted phenyl 3-pyridyl ketones with "nonstabilized" phosphorus ylides which contain a carboxyl terminus preferentially forms the (*E*)-olefin. The preference for this stereoselectivity stems from either hydrogen bonding or salt-bridge formation between the amide group and the carboxyl terminus during formation of the oxaphosphetane intermediate.

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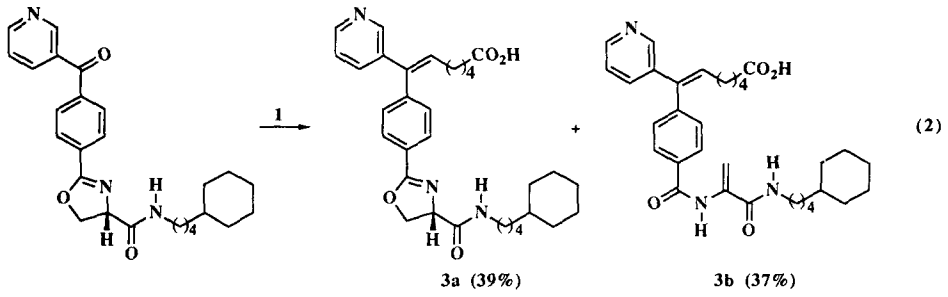
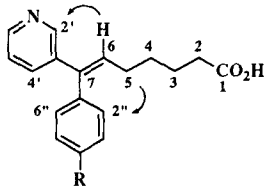
6. Ring opening of the oxazoline took place via β-elimination by the excess base employed during the Wittig olefination reaction (eq 2). It is difficult to say which reaction was taking place faster: Wittig olefination or β-elimination? The products **3a** and **b** were nonetheless enriched by the (*E*)-isomer).



(2)

7. 4-[[(4-Cyclohexylbutyl)amino]carbonyl]phenyl 3-pyridyl ketone was prepared in 4 steps (56%) from commercially available methyl 4-formylbenzoate: (1) nucleophilic addition of 3-lithiopyridine in Et_2O at -78 °C to rt; (2) MnO_2 oxidation of the resulting phenyl pyridyl carbinol in THF at reflux; (3) hydrolysis of the ester (1.0 N NaOH, THF); and (4) amide coupling with 4-cylohexylbuylamine.

8. The yield and *E*:*Z* ratio of **8a** (Table I) were determined as its methyl ester since purification of acid **8a** was difficult due to contamination by a byproduct, $Ph_2P(O)(CH_2)_5CO_2H$, generated from the Wittig salt during the reaction. The stereochemistry of the double bond geometry of the Wittig products was determined using ROESY and/or difference NOE experiments. In the major isomer there was an NOE between the following pairs of resonances: H-6 and H-2'/H-4'; H-5 and H-2"/H-6". These data established the syn configuration of C-5 and the phenyl ring to be on the same side of the double bond, i.e., the major product was an (*E*)-isomer.



9. 4-Acetamidophenyl 3-pyridyl ketone was prepared in two steps (8%) from commercially available 4-acetamidobenzaldehyde: (1) nucleophilic addition of 3-lithiopyridine in Et_2O at -78 to 7 °C; and (2) MnO_2 oxidation of the resulting phenyl pyridyl carbinol in THF at reflux.

10. Satisfactory spectral and analytical data were obtained for all the compounds prepared. For example, **10** (light yellow foam): ^1H NMR (DMSO) δ 7.53 (br s, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.51 (m, 1H), 6.27 (d, J = 8.4 Hz, 2H), 5.36 (t, J = 7.5 Hz, 1H), 1.40-1.27 (m, 4H), 1.31 (s, 3H), 0.80 - 0.65 (m, 4H); IR (KBr) 1696, 1670 (CO); FDMS 338 (M+). Anal. Calcd for $C_{20}H_{22}N_2O_3 \cdot 0.3C_2H_4O_2$: C, 69.42; H, 6.56; N, 7.86. Found: C, 69.34; H, 6.72; N, 7.70.