T₃P- A Novel Catalyst for Aza-Diels-Alder Reaction: One-Pot Synthesis of Pyrano [3,2-*c*]quinolines and furano[3,2-*c*]quinolines

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Abstract: T₃P was found to be an efficient catalyst for the Aza-Diels–Alder reactions of aldimines with dihydropyran or dihydrofuran to afford the corresponding pyrano-and furo [3,2-*c*]quinolines in high yields with high diastereoselectivity in a short period of time

Keywords: Aza-Diels–Alder reactions, T₃P, Pyrano- and Furo-quinolines

Introduction

One of the most powerful methods to synthesise nitrogen containing six membered heterocycles is the classical Aza-Diels–Alder reaction¹. The pyranoquinoline and furanoquinolines are a class of nitrogen containing heterocycles which are synthesized by Aza-Diels–Alder methodology. Whereas pyranoquinolines exhibit biological properties such as psychotropic, antiallergic, anti-inflammatory and estrogenic activities in addition to their use as pharmaceuticals², the furanoquinolines function as antagonists of 5-hydroxytryptamine receptors in animals and have been found to be most potent anti-inflammatory agents in addition to being the most potent anti-inflammatory agents³. Generally these compounds are prepared by Aza-Diels–Alder reactions of imines derived from aldehydes and amines with dihydropyran or dihydrofuran using transition-metal complexes such as Co₂(CO)₈, Ni(CO)₄⁴ and InCl₃,⁵ the most common⁶ being BF₃.OEt₂. Several other methods reported in the literature use GdCl₃, ZrCl₄, LiClO₄, LiBF₄, I₂ and montmorillonite clay to promote this reaction⁷.

Propylphosphonic anhydride(T₃P) is an highly reactive *n*-propyl phosphonic acid cyclic anhydride, generally used as coupling agent and water scavenger with low toxicity and low allergenic potential⁸. Broad functional group tolerance, low epimerization tendency, easy work up due to water soluble side products make the reagent one among the potential class of reagents for diverse transformations⁹⁻¹⁴.

Owing to the attractive and potential biological activities of pyrano- and furo-quinolines, novel, mild and more efficient one-pot protocol for the synthesis of these compounds are still in great demand and herein we wish to explore T3P as novel catalyst to synthesize these compounds.

Experimental

All the chemicals used are of commercial grade and were used without further purification. The products were characterized by comparison of their physical data with those of known samples or by comparison of their IR, ¹H NMR and LC-mass spectra.

Preparation of pyrano[3,2-c]quinolines and furano[3,2-c]quinolines; General experimental procedure

To a stirred solution of the benzaldehyde (1 mmol), aniline (1 mmol), and 3,4-dihydro-2H-pyran or 2,3-dihydrofuran (1 mmol) in THF (10 mL), T₃P (0.2 mmol) was added and the mixture stirred at room temperature for the specified time (Table 1). After completion (followed by TLC), the solvent was removed under reduced pressure using a rotary evaporator. The crude material was subjected to column chromatography over silica gel eluting with Hexane–EtOAc (2–10%) to afford the pure pyrano- or furoquinolines. The known compounds were identified by comparison of spectral data and mp with those reported.

Selected spectral data of selected compounds

cis-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]-quinoline (4a)

White Solid, m.p. 130–132 °C, IR (KBr): ν 3341, 2977, 2853, 1606, 1489, 1092 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.24–7.44 (m, 6H), 7.00 (t, 1H, J = 7.7 Hz), 6.76 (t, 1H, J = 7.9 Hz), 6.54 (d, 1H, J = 8 Hz), 5.29 (d, 1H, J = 5.7 Hz), 4.67 (d, 1H, J = 2.5 Hz), 3.77 (br s, 1H), 3.53 (dd, 1H, J = 11.2, 2.3 Hz), 3.40 (dt, J = 11.2, 2.3 Hz), 2.14–2.18 (m, 1H), 1.49–1.69 (m, 1H), 1.23 (m, 1H) EIMS m/z (%): 265 (M⁺). Anal. Calcd for C₁₈H₁₉NO (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.51; H, 7.34; N, 5.32.

trans-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]-quinoline (4a)

Yellow Oil, IR (neat): ν 3327, 2943, 2866, 1603, 1482, 1083 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.44–7.54 (m, 6H), 7.21 (d, 1H, J = 8.0 Hz), 7.0 (t, 1H, J = 7.9 Hz), 6.74 (t, 1H, J = 8 Hz), 5.49 (d, 1H, J = 7.6 Hz), 4.77 (d, 1H, J = 10.3 Hz), 4.41 (d, 1H, J = 2.3 Hz), 4.01–4.11 (m, 2H), 3.76 (dt, J = 11.4, 2.3 Hz), 2.14–2.24 (m, 2H), 1.81–1.91 (m, 1H), 1.23–1.55 (m, 3H) EIMS m/z (%): 265 (M⁺). Anal. Calcd for C₁₈H₁₉NO (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.54; H, 7.36; N, 5.35.

Results and Discussion

Coupling of aldehydes, amines and enol ethers in Aza-Diels–Alder reaction produces stoichiometric amount of water which decomposes many of the Lewis acids used for the reaction. To circumvent the problem we wanted to use T₃P a well known water scavenger to catalyse the same reaction. In a typical procedure, benzaldehyde, aniline and 3,4-dihydro-2H-pyran were reacted in the presence of catalytic amount of T₃P (20 mol. %) in tetrahydrofuran (THF) at room temperature. To our surprise the reaction yielded the corresponding pyrano[3,2-c]quinoline within 30 min as a mixture of cis- and trans- isomers in the ratio of 22:78, in an overall yield of 90%. Easy separation of the isomers was achieved by

chromatography over silica gel (Scheme 1). We could establish the structures of these isomers based on ^1H NMR data.

Scheme 1

Encouraged by the initial observation, various benzaldehydes and anilines were reacted with dihydropyran, to check the efficiency of T₃P to catalyse the reaction and the generality of the methodology. All the reactions involving various aldehydes containing electron donating and electron withdrawing substituents formed imine *in situ* and the imine reacted with dihydropyran, to give the corresponding pyranoquinolines. We could achieve high yields and high diastereoselectivity. The results are listed in Table 2. Simultaneously the ratio of the isomers obtained in each reaction was determined from the ^1H NMR spectrum of the crude product and the structures of the products were established on the basis of spectroscopic (IR, ^1H NMR, ^{13}C NMR and MS) data of the pure compounds from column chromatography. To further optimize the reaction condition in terms of solvent and catalyst loading we tried the reaction in various solvents and also without solvent and various mmols of the catalyst. The results are summarized in Table 1.

Table 1. Optimisation of catalytic and solvent condition on the reaction of aniline, benzaldehyde and 3,4-dihydro-2H-pyran^a.

Entry	Solvent	Catalyst, mmole	Time, min	Yield, % ^b	Product trans:cis) ^c
1	CHCl ₃	0.2	30	61	60:30
2	CH ₂ Cl ₂	0.2	30	63	64:36
3	CH ₃ CN	0.2	30	68	68:32
4	Toluene	0.2	30	59	60:40
5	None	0.2	60	55	63:37
6	THF	0.2	30	90	22:78
7	THF	0.1	60	72	24:76
8	THF	0.3	60	87	23:73
9	THF	0.4	60	86	24:76

^aReaction Conditions: Benzaldehyde (1 mmol), aniline (1 mmol) and 3,4-dihydro-2H-pyran (1 mmol) in solvent (10 mL), room temperature. ^bIsolated Yield. ^cRatio of the product was determined from the crude ^1H NMR spectra

Since the methodology will not be completed by itself if we could not extend it to the synthesis of furo-quinolines we exploited the reactivity of dihydrofuran with benzaldehydes and anilines catalyzed by T₃P. The reaction proceeded in a short period of time and afforded

the corresponding furo[3,2-c]quinolines as cis/trans mixtures, which could be separated by column chromatography over silica gel (Scheme 2) and the results are listed in Table 2. The structures of these compounds were also characterized by IR, ¹H NMR and MS spectral data, and were also compared with the data of compounds reported in the literature.

Scheme 2

Table 2. T₃P-Catalyzed synthesis of pyrano- and furoquinolines

Entry	Aniline	Benzaldehyde	Olefin	Time, min	Yield, %	Product Ratio ^a 4:5 or 6:7
a	Aniline	Benzaldehyde	Dihydropyran	30	90	22:78
b	Aniline	4-Chloro	Dihydropyran	30	87	24:76
c	Aniline	4-Methoxy	Dihydropyran	30	83	20:80
d	Aniline	3-Nitro	Dihydropyran	30	80	25:75
e	4-Fluoro	4-Chloro	Dihydropyran	30	79	28:72
f	4-Bromo	Benzaldehyde	Dihydropyran	30	80	25:75
g	Aniline	Benzaldehyde	Dihydropyran	30	90	16:84
h	Aniline	4-Bromo	Dihydropyran	30	85	26:74
i	4-Methoxy	4-Chloro	Dihydropyran	30	83	28:72
j	Aniline	2-Chloro,5-Nitro	Dihydropyran	30	82	21:80

^a isomer ratios were calculated based on ¹H NMR spectra of the crude products

Conclusion

In conclusion, we have demonstrated T₃P as an effective catalyst for the Aza-Diels-Alder reaction to afford pyrano- and furo-quinolines in good yields, under mild reaction conditions, with high diastereoselectivity.

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