© 2018 IJSRSET | Volume 4 | Issue 1 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section : Engineering and Technology

An Efficient Protocol for Acid-Amine Coupling using T3P as Coupling Agent

Arpit C. Radadia[1], Jaydip G. Rajpara[1], Rajendra Jadav[2], Yogesh T. Naliapara[*1]
[*1]Department of Chemistry, Saurashtra University, Rajkot, Gujarat, India
[2]Bhavans Science College,Ahemdabad, Gujarat. India

ABSTRACT

Amide bond is prevalent in peptides. Moreover, at least 25% pharmaceutical products also contain amide bond. Acid amine coupling of 4-(4-aminophenyl)morpholin-2-one with different acids has been synthesized in presence of T_3P (Propylphosphonic anhydride), DIPEA base with Ethyl acetate as a solvent at room temperature for 30 mins to yield N-(4-(2-oxomorpholino)phenyl)-2-phenylquinoline-4-carboxamide derivatives.

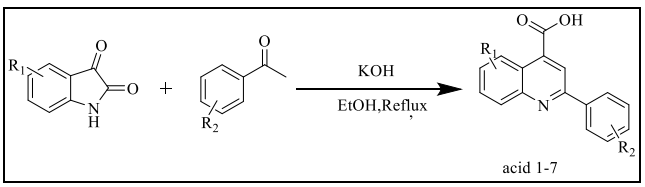
Keywords: Acid-Amine Coupling, T_3P (Propylphosphonic Anhydride), Quinolone 4 Carboxylic Acid

I. INTRODUCTION

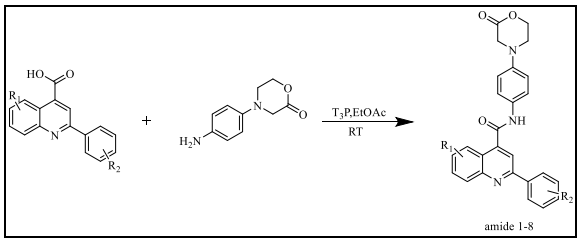
Numerous small and large peptides, which are sequence and length-specific polymers composed of amino acids, represent compounds with significant therapeutic applications. Peptides and their higher relatives proteins play a crucial role in almost all processes of the living cell. Representative examples include somatostatin, substance P, cholecystokinin, endorphin, enkephalin, angiotensin II and endothelin. As neurotransmitters, neuromodulators and hormones peptides are responsible for the regulation of biochemical processes in complex organisms such as cell-cell communication and control of vital functions like metabolism, immune response, digestion, respiration, sensitivity to pain, reproduction, behaviour and electrolyte levels. Since so many of peptides possess potent pharmacological properties, they are of enormous medicinal interest.Quinoline[1] 1-aza-napthalene and benzo[b]pyridine are nitrogen containing heterocyclic aromatic compounds. Quinolines are very important compounds due to the ir wide spectrum of biological activities behaving as anti-malarial, anti-bacterial, antifungal, anti-asthmatic, anti-hypertensive, anti-inflammatory, antiplatelet activity[2–9]. In addition quinolines have been employed in the study of bioorganic and bio organo-metallic processes[10,11]. Considering the significant applications in the fields of medicinal, bioorganic, industrial, and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinolines. Some derivatives of such as quinoline-4-carboxylic acid elicited profound changes in the morphology of typical tips of Botrytis cinerea[12] Quinoline-4-carboxylic acids are one of the most important series of quinoline derivatives because they exhibit a wide variety of medicinal effects and are applied as active components in industrial antioxidants[13,14]. Meanwhile, quinoline-4-carboxylic acids are the key precursors for the synthesis of other useful quinoline derivatives[15]. Despite remarkable efforts in the last decade[16–19] the development of effective methods for the synthesis of quinoxaline ring is still an important challenge and much in demands. In recent years, many methods for the synthesis of these quinoline acids have successively been reported. The conventional synthesis involves the Pfitzinger reaction [20,21]. Doebner reaction[22], Friedlander and Combes methods[23–29]. However, these synthetic methods require expensive and hazardous solvents and chemicals, as well as harsh reaction condition. Therefore, the development of simple, convenient, and environmentally benign approaches for the synthesis of quinolines is still desirable.

II. RESULT AND DISCUSSION

Scheme 1. Synthesis of 2-arylquinoline-4-carboxylic acid

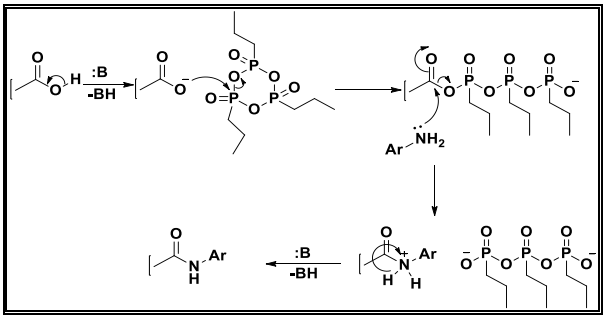


Scheme-2. Synthesis of N-(4-(2-oxomorpholino)phenyl)-2-phenylquinoline-4-carboxamide

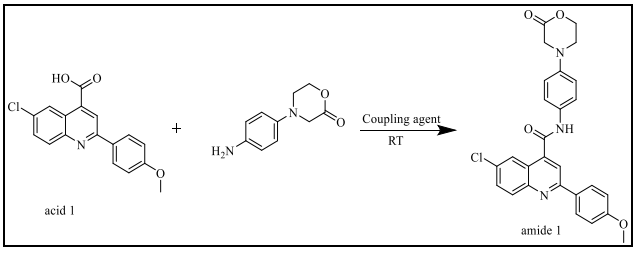


2-arylquinoline-4-carboxylicacid were synthesized by refluxing Isatin and substituted acetophenones in methanolic NaOH solution for 5-6h. Peptide coupling of 2-arylquinoline-4-carboxylic acids and 4-(4-aminophenyl)morpholin-2-one was carried out in presence of T_3P(propyl phosphonic anhydride) and DIPEA by using ethylacetate as solvent(Scheme 2).

By using this method eight analogues have been synthesized. Different substitution were used is listed in Table 1. A mechanism of peptide coupling by T3P is demonstrated in Scheme 3 as shown below**.**



we are investigate best coupling agent among all coupling agent as shown below model subtract.



Entry	Coupling agent	Solvent	Yield
1	DCC	MDC	45
2	HATU	THF	60
3	T_3P	EtOAc	88
4	HBTU	THF	65
5	TBTU	THF	76

As shown in above table we have find T_3P is best coupling reagent among other reagent.

Table 1

Entry	$-R_1$	$-R_2$	Yield(%)
AAC 1	-Cl	$-4OCH_3$	76
AAC 2	-Cl	-4F	78
AAC 3	-H	-4OH	74
AAC 4	-H	3,4 dimethoxy	88
AAC 5	-Cl	$-3NH_2$	87
AAC 6	-Cl	$-4CH_3$	65
AAC 7	-H	-3Cl	80

Experimental Section

General procedure for the synthesis of 2-arylquinoline-4-carboxylic acid(acid-1-7).

Isatin(50 mmol) was added portionwise to the methanolic-NaOH solution(250 mmol in 50 ml methanol) in icebath. At the same temperature substituted acetophenone(50 mmol) was added. Reaction mixture was then refluxed for 5-6 h. After completion of reaction, mixture was poured in to ice-water. Suspended residue was filtered. Filtrate was acidified with con. HCl. Precipitated solid was filtered and washed with water. This solid (acid-1-7) was used in next step without further purification.

General procedure for the synthesis of of N-(4-(2-oxomorpholino)phenyl)-2-phenylquinoline-4-carboxamide (AAC-1-7).

To the suspension of acid-1-7(2 mmol) and 4-(4-aminophenyl)morpholin-2-one (2mmol) in ethylacetate, T_3P(2.2 mmol) was added drop wise at 100C. Immediately diisopropylethylamine(4.4 mmol) was added also drop wise at the same temperature. Reaction mixture was allowed to stirred at RT for 30 min. Progress of the reaction was monitored by TLC (Methanol:MDC 0.5:9.5 ml). After completion of reaction, reaction mixture was poured in to water and extracted with ethylacetate. Extracted organic layer was dried over sodium sulphate and concentrated under vacuum. Product was purify by column chromatography using neat MDC to afford pure Amide-1 to 7.

Spectral Data of Synthesized Compound

6-chloro-2-(4-methoxyphenyl)-N-(4-(2-oxomorpholino)phenyl)quinoline-4-carboxamide

^{1}H NMR (500 MHz, Chloroform) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 4H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.29 (s, 2H), 7.25 (d, *J* = 7.5

Hz, 4H), 7.10 – 7.01 (m, 6H), 6.68 (d, *J* = 7.5 Hz, 4H), 4.49 (s, 2H), 4.42 (dd, *J* = 13.5, 8.9 Hz, 6H), 3.87 – 3.76 (m, 10H). Chemical Formula: $C_{27}H_{22}ClN_3O_4$;M.W: 487.94Elemental Analysis: C, 66.46; H, 4.54; Cl, 7.27; N, 8.61; O, 13.12

6-chloro-2-(4-fluorophenyl)-N-(4-(2-oxotetrahydro-2H-pyran-4-yl)phenyl)quinoline-4-carboxamide

^{1}H NMR (500 MHz, Chloroform) δ 8.48 (d, *J* = 1.6 Hz, 2H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.98 – 7.90 (m, 4H), 7.82 (s, 2H), 7.64 (dd, *J* = 7.5, 1.4 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 4H), 7.31 (d, *J* = 7.5 Hz, 4H), 7.27 (s, 2H), 7.16 (t, *J* = 7.7 Hz, 4H), 4.41 (dt, *J* = 12.4, 5.1 Hz, 2H), 4.31 (dt, *J* = 12.3, 5.1 Hz, 2H), 3.35 (p, *J* = 3.5 Hz, 2H), 2.92 (d, *J* = 3.5 Hz, 1H), 2.90 (d, *J* = 3.5 Hz, 1H), 2.62 (d, *J* = 3.7 Hz, 1H), 2.60 (d, *J* = 3.5 Hz, 1H), 2.50 (dtd, *J* = 12.5, 5.2, 3.2 Hz, 2H), 2.28 (dtd, *J* = 12.5, 5.2, 3.2 Hz, 2H).Chemical Formula: $C_{27}H_{20}ClFN_2O_3$;M.W: 474.92Elemental Analysis: C, 68.29; H, 4.24; Cl, 7.46; F, 4.00; N, 5.90; O, 10.11

2-(4-hydroxyphenyl)-N-(4-(2-oxotetrahydro-2H-pyran-4-yl)phenyl)quinoline-4-carboxamide

^{1}H NMR (500 MHz, Chloroform) δ 8.64 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.08 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.84 (s, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.28 (s, 1H), 6.91 (d, *J* = 7.5 Hz, 2H), 4.41 (dt, *J* = 12.4, 5.1 Hz, 1H), 4.32 (dt, *J* = 12.4, 4.9 Hz, 1H), 3.97 (s, 1H), 3.12 – 3.01 (m, 1H), 2.87 (dd, *J* = 12.4, 8.5 Hz, 1H), 2.57 (dd, *J* = 12.4, 8.5 Hz, 1H), 2.47 (ddt, *J* = 12.3, 7.3, 4.9 Hz, 1H), 2.18 (ddt, *J* = 12.3, 7.3, 4.9 Hz, 1H);Chemical Formula: $C_{27}H_{22}N_2O_4$;M.W:438.48;Elemental Analysis: C, 73.96; H, 5.06; N, 6.39; O, 14.59.

2-(3,4-dimethoxyphenyl)-N-(4-(2-oxomorpholino)phenyl)quinoline-4-carboxamide

Chemical Formula: $C_{28}H_{25}N_3O_5$

Molecular Weight: 483.52

Elemental Analysis: C, 69.55; H, 5.21; N, 8.69; O, 16.54

6-chloro-N-(4-(2-oxotetrahydro-2H-pyran-4-yl)phenyl)-2-(p-tolyl)quinoline-4-carboxamide

Chemical Formula: $C_{28}H_{23}ClN_2O_3$

Molecular Weight: 470.95

Elemental Analysis: C, 71.41; H, 4.92; Cl, 7.53; N, 5.95; O, 10.19

III. CONCLUSION

We have described the modified and more convenient method for the synthesis of N-(4-(2-oxomorpholino)phenyl)-2-phenylquinoline-4-carboxamide. The method of acid-amine coupling by using T_3P is more superior than other method. All the novel compounds described in Table 1 are well characterized by mass, ^{1}H NMR and ^{13}C NMR spectroscopy. From the result of cytotoxicity, it reveals that the synthesized compounds are effective at higher concentration. In summary, we have demonstrated a simple route for the synthesis of amide containing compound using T_3P in ethyl acetate as an efficient catalyst. The use of T_3P was well tolerated with a range of amine. This protocol is general and provides peptide derivatives in good to excellent yields depending on the reactivity of acid and amine. Thus, the present synthesis of peptide bond will serve as an exclusive method of preparative importance for this class of compounds.

IV. REFERENCES

[1]. Abadi, A. H. ; Hegazy, G. H. ; El-Zaher, A. A. Bioorg. Med. Chem. 2005, 13 20), 5759.

[2]. Larsen, R. D. ; Corley, E. G. ; King, A. O. ; Carroll, J. D. ; Davis, P. ; Verhoeven, T. R. ; Reider, P. J. ; Labelle, M. ; Gauthier, J. Y. ; Xiang, Y. Bin. J. Org. Chem. 1996, 61 10), 3398.

[3]. Chen, Y. -L. ; Fang, K. -C. ; Sheu, J. -Y. ; Hsu, S. -L. ; Tzeng, C. -C. J. Med. Chem. 2001, 44 14), 2374.

[4]. Braccio, R. G. Eur. J. Med. Chem 2000, 35, 1021.

[5]. Kalluraya, B. ; Sreenivasa, S. Farm. 1998, 53 6), 399.

[6]. Dubé, D. ; Blouin, M. ; Brideau, C. ; Chan, C. -C. ; Desmarais, S. ; Ethier, D. ; Falgueyret, J. -P. ; Friesen, R. W. ; Girard, M. ; Girard, Y. Bioorg. Med. Chem. Lett. 1998, 8 10), 1255.

[7]. Ferrarini, P. L. ; Mori, C. ; Badawneh, M. ; Manera, C. ; Martinelli, A. ; Romagnoli, F. ; Saccomanni, G. ; Miceli, M. J. Heterocycl. Chem. 1997, 34 5), 1501.

[8]. Maguire, M. P. ; Sheets, K. R. ; McVety, K. ; Spada, A. P. ; Zilberstein, A. J. Med. Chem. 1994, 37 14), 2129.

[9]. Ko, T. -C. ; Hour, M. -J. ; Lien, J. -C. ; Teng, C. -M. ; Lee, K. -H. ; Kuo, S. -C. ; Huang, L. -J. Bioorg. Med. Chem. Lett. 2001, 11 3), 279.

[10]. Nakatani, K. ; Sando, S. ; Saito, I. Bioorg. Med. Chem. 2001, 9 9), 2381.
[11]. He, C. ; Lippard, S. J. Inorg. Chem. 2001, 40 7), 1414.
[12]. Strigáčová, J. ; Hudecova, D. ; Lásiková, A. ; Végh, D. Folia Microbiol. Praha). 2000, 45 4), 305.
[13]. Michael, J. P. Nat. Prod. Rep. 2005, 22 5), 627.
[14]. Michael, J. P. Nat. Prod. Rep. 2004, 21 5), 650.
[15]. Xiang, Y. Y. ; Hill, J. M. ; Yu, G. ; Yang, Y. ; Kluge, A. F. ; Keith, D. ; Finn, J. ; Gallant, P. ; Silverman, J. ; Lim, A. Bioorg. Med. Chem. Lett. 2001, 11 4), 541.
[16]. Gobec, S. Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; Thieme/Houben-Weyl Series, 2003; Vol. 16.
[17]. Kim, S. Y. ; Park, K. H. ; Chung, Y. K. Chem. Commun. 2005, No. 10, 1321.
[18]. Bassoude, I. ; Berteina-Raboin, S. ; Leger, J. -M. ; Jarry, C. ; Essassi, E. M. ; Guillaumet, G. Tetrahedron 2011, 67 12), 2279.
[19]. Antoniotti, S. ; Duñach, E. Tetrahedron Lett. 2002, 43 22), 3971.
[20]. Buu-Hoi, N. P. ; Xuong, N. D. ; Lavit, D. J. Org. Chem. 1953, 18 8), 910.
[21]. Atwell, G. J. ; Baguley, B. C. ; Denny, W. A. J. Med. Chem. 1989, 32 2), 396.
[22]. Allen, C. F. H. ; Spangler, F. W. ; Webster, E. R. J. Org. Chem. 1951, 16 1), 17.
[23]. Attanasi, O. A. ; De Crescentini, L. ; Filippone, P. ; Foresti, E. ; Galezzi, R. ; Ghiviriga, I. ; Katritzky, A. R. Tetrahedron 1997, 53 15), 5617.
[24]. Cho, C. S. ; Oh, B. H. ; Kim, J. S. ; Kim, T. -J. ; Shim, S. C. Chem. Commun. 2000, No. 19, 1885.
[25]. Jiang, B. ; Si, Y. -G. J. Org. Chem. 2002, 67 26), 9449.
[26]. Manske, R. H. F. ; Kulka, M. Org. React. 1953.
[27]. Yadav, J. S. ; Reddy, B. V. S. ; Premalatha, K. Synlett 2004, 2004 6), 963.
[28]. Thomas, A. ; Chakraborty, M. ; Ila, H. ; Junjappa, H. Tetrahedron 1990, 46 2), 577.
[29]. Theoclitou, M. -E. ; Robinson, L. A. Tetrahedron Lett. 2002, 43 21), 3907.