An Efficient Three-Component Synthesis of 3-(1-Hydroxyalkyl)[1,2,4]-triazolo[4,3-*c*]quinazolines

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Abstract: An efficient three-component synthesis of 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines is described. A mixture of *N*-isocyaniminotriphenylphosphorane, an aldehyde, and a 4(3*H*)-quinazolinone undergo a 1:1:1 addition reaction in refluxing THF to afford the title compounds in good to excellent yields.

Key words: *N*-isocyaniminotriphenylphosphorane, 4(3*H*)-quinazolinones, aldehydes, 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines, multicomponent reactions, cyclizations, heterocycles

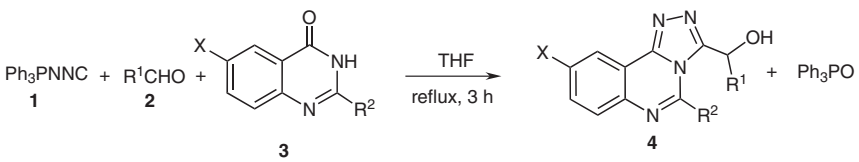
Multicomponent reactions (MCR) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCR is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCR, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'druglike' molecules. The isocyanide-based MCR are especially important in this area.[1d,e]

Fused bridgehead heterocycles, [1,2,4]triazolo[4,3-*c*]quinazolines,[2,3] constitute an important class of heterocyclic compounds with interesting biological properties, some of which have been shown to possess anticancer,[4] anti-inflammatory,[5,6] and antibacterial[7] activities. Some examples have exhibited hypotensive[6] and hypertensive[8] properties. Other examples are highly selective agonists or antagonists for GABAa brain receptors and are useful in the diagnosis and treatment of anxiety, sleep, seizure disorders, and also enhancement of memory.[9]

The most common approaches for the preparation of [1,2,4]triazolo[4,3-*c*]quinazolines involve condensation–cyclization of 2-(2-aminophenyl)-1,2,4-triazoles with carboxylic acids or acid chlorides;[10] cyclization of 4-hydrazinoquinazolines with one-carbon cyclizing reagents such as carboxylic acids or acid chlorides,[5b] carbon disulfide,[5a,11] or orthoesters;[6,12] cyclization of quinazolin-4-ylhydrazones and quinazolin-4-ylhydrazides;[5a,11] and reaction of 4-chloroquinazoline with tetrazoles.[13]

There are several reports on the use of *N*-isocyaniminotriphenylphosphorane (**1**, $CNNPPh_3$, Scheme 1) in the synthesis of metal complexes.[14,15] However, applications of **1** in organic synthesis are rare. Recently, a synthesis of 1,3,4-oxadiazepines via a three-component reaction between **1**, dialkyl acetylenedicarboxylates, and 1,3-diphenyl-1,3-propanedione[16] and a synthesis of 2-aryl-1,3,4-oxadiazoles from **1** and benzoic acids[17] were reported. Very recently, we have reported a new synthesis of 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles via a one-pot and three-component reaction between **1**, aldehydes, and carboxylic acids.[18]

Knowing the pharmacological importance of the [1,2,4]triazolo[4,3-*c*]quinazoline ring systems, we have recently focused on introducing a new synthesis of this nucleus bearing in mind previously reported synthetic routes. As part of our current studies on the development of efficient and simple synthesis of biologically active heterocyclic compounds,[19] herein we describe a new, one-pot, and three-component synthesis of [1,2,4]triazolo[4,3-*c*]quinazolines. Thus a mixture of *N*-isocyaniminotriphenylphosphorane (**1**), an aldehyde **2**, and a 4(3*H*)-quinazolinone **3** undergo a 1:1:1 addition reaction in refluxing THF to produce the corresponding 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines **4a–l** in 84–97% yields (Scheme 1, Table 1). All the reactions reached completion within three hours. ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of the corresponding [1,2,4]triazolo[4,3-*c*]quinazolines **4** in good to



Scheme 1

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excellent yields. Any product other than **4** and triphenylphosphine oxide could not be detected by NMR spectroscopy.[20]

The structures of the isolated products were deduced on the basis of IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **4f** displayed the molecular ion [M$^+$] peak at *m/z* = 411 which was consistent with the 1:1:1 adduct of *N*-isocyaniminotriphenylphosphorane, 2-(4-methylphenyl)-4(3*H*)-quinazolinone, and 4-nitrobenzaldehyde losing triphenylphosphine oxide. The IR spectrum of **4f** showed an absorption at 3344 cm^{-1} indicating the presence of a hydroxy group. The ^{1}H NMR spectrum of **4f** exhibited a sharp singlet at δ = 2.42 ppm due to the methyl group. Two doublets were seen for the mutually coupled aliphatic methine H atom (δ = 5.52 ppm, *J* = 5.8 Hz) and the adjacent hydroxy group (δ = 6.25 ppm, *J* = 5.8 Hz). The characteristic multiplets for the twelve H atoms of the two aryl substituents and the phenylene moiety were seen with appropriate chemical shifts and coupling constants. The ^{1}H-decoupled ^{13}C NMR spectrum of **4f** showed characteristic signals at δ = 21.12 (due to CH_3), 65.77 ppm (arising from CH), along with other 17 distinct resonances (8 CH and 9 C) in agreement with the proposed structure.[20]

A plausible mechanism for the reaction is provided in Scheme 2. On the basis of the well-established chemistry of isocyanides,[1d,e,21–23] it is reasonable to assume that the first step could involve nucleophilic addition of the isocyanide **1** on the aldehyde **2** and subsequent protonation of the alkoxide intermediate **5** by the NH-acid **3**, leading to the nitrilium intermediate **6**. This positively charged intermediate may be attacked by the conjugate base of the acid **7** to form the adduct **8**. This adduct may undergo intramolecular aza-Wittig reaction of the iminophosphorane moiety with the amide carbonyl to afford the isolated 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines **4** by removal of triphenylphosphine oxide from betaine intermediate **9**.

Table 1 Synthesis of 3-(1-Hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]-quinazolines **4a–l**

4	X	R^1	R^2	Yield (%)[a]
4a	H	Ph	Ph	92
4b	H	Ph	4-MeC_6H_4	93
4c	H	4-FC_6H_4	Ph	93
4d	H	3-ClC_6H_4	Ph	94
4e	H	4-MeOC_6H_4	Ph	88
4f	H	4-O_2NC_6H_4	4-MeC_6H_4	97
4g	H	4-MeC_6H_4	Ph	90
4h	H	4-O_2NC_6H_4	Bn	96
4i	H	4-FC_6H_4	Bn	95
4j	H	4-O_2NC_6H_4	PhCH_2CH_2	91
4k	H	*n*-Pr	Ph	84
4l	Cl	Ph	Ph	90

[a] Isolated yield.

In conclusion, we have developed a new, one-pot, and three-component reaction between *N*-isocyaniminotriphenylphosphorane, aldehydes, and 4(3*H*)-quinazolinones for the efficient synthesis of 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines, which are of potential synthetic and pharmacological interest. The reactions were performed under neutral conditions. The simplicity of this method makes it an interesting alternative to other [1,2,4]triazolo[4,3-*c*]quinazoline syntheses. 3-(1-Hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines prepared in the present study may find useful applications in synthetic organic, bioorganic, and medicinal chemistry.

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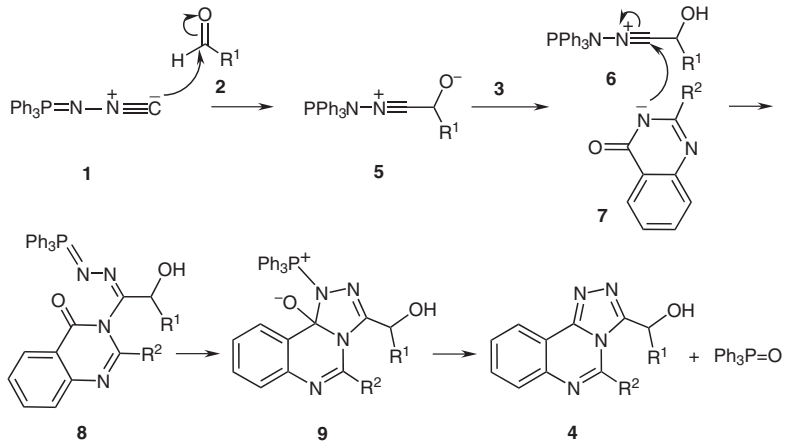

Scheme 2

References and Notes

(1) (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley: Weinheim, **2005**. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575. (c) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (e) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

(2) Shaban, M. A. E.; Nasr, A. Z. *Synthesis of Condensed 1,2,4-Triazolo[3,4-x]heterocycles,* In *Advances in Heterocyclic Chemistry*, Vol. 49; Katritzky, A. R., Ed.; Academic Press: New York, **1990**, 335–337.

(3) Hajós, G.; Riedl, Z. In *Comprehensive Heterocyclic Chemistry III*, Vol. 11; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier Science: Oxford, **2008**, Chap. 16, 671–762; and references therein.

(4) (a) Cipak, L.; Letasiova, S.; Repicky, A.; Jantova, S. *Neoplasma* **2007**, *54*, 16. (b) Jantová, S.; Letasiová, S.; Repický, A.; Ovádeková, R.; Lakatos, B. *Cell. Biochem. Funct.* **2006**, *24*, 519.

(5) (a) Mohamed, M. S.; Ibrahim, M. K.; Alafify, A. M.; Abdel-Hamide, S. G.; Mostafa, A. M. *Int. J. Pharmacol.* **2005**, *1*, 261. (b) Gineinah, M. M.; Nasr, M. N.; Abdelal, A. M.; El-Emam, A. A.; Said, S. A. *Med. Chem. Res.* **2000**, *10*, 243.

(6) Hardtmann, G. E.; Kathawala, F. G. US 4,053,600, **1977**; *Chem. Abstr.* **1978**, *88*, 22970k.

(7) (a) Jantová, S.; Špirková, K.; Stankovský, Š.; Duchonová, P. *Folia Microbiol. (Praha)* **1999**, *44*, 187. (b) Jantová, S.; Stankovský, Š.; Špirková, K. *Biol. Brat.* **2004**, *59*, 741.

(8) Hardtmann, G. E.; Kathawala, F. G. DE 2,261,095 (A1), **1973**; *Chem. Abstr.* **1973**, *79*, 66385s (A).

(9) Chen, P.; Hutchison, A. US 5,677,309 (A), **1999**; *Chem. Abstr.* **1997**, *127*, 346408p.

(10) Hergenrother, P. M. *J. Heterocycl. Chem.* **1972**, *9*, 131.

(11) (a) Sidhu, G. S.; Thyarajan, G.; Rao, N. *Naturwissenschaften* **1963**, *50*, 732. (b) Spirkova, K.; Stankovsky, S.; Dandarova, M. *Collect. Czech. Chem. Commun.* **1994**, *59*, 222. (c) Spirkova, K.; Stankovsky, S.; Hornacek, J. *Collect. Czech. Chem. Commun.* **1994**, *59*, 243.

(12) Breuer, H. *Tetrahedron Lett.* **1976**, *17*, 1935.

(13) Huisgen, R.; Sturm, H. J.; Seidel, M. *Chem. Ber.* **1961**, *94*, 1555.

(14) Stolzenberg, H.; Weinberger, B.; Fehlhammer, W. P.; Pühlhofer, F. G.; Weiss, R. *Eur. J. Inorg. Chem.* **2005**, *21*, 4263.

(15) Chiu, T. W.; Liu, Y. H.; Chi, K. M.; Wen, Y. S.; Lu, K. L. *Inorg. Chem.* **2005**, *44*, 6425.

(16) Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett.* **2007**, *48*, 2617.

(17) Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549.

(18) Adib, M.; Riazati Kesheh, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2009**, 1575.

(19) (a) Adib, M.; Sheibani, E.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2008**, *64*, 10681. (b) Adib, M.; Sayahi, M. H.; Ziyadi, H.; Zhu, L. G.; Bijanzadeh, H. R. *Synthesis* **2008**, 3289. (c) Adib, M.; Mohammadi, B.; Bijanzadeh, H. R. *Synlett* **2008**, 3180. (d) Adib, M.; Mohammadi, B.; Bijanzadeh, H. R. *Synlett* **2008**, 177. (e) Adib, M.; Sayahi, M. H.; Ziyadi, H.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2007**, *63*, 11135. (f) Adib, M.; Aali Koloogani, S.; Abbasi, A.; Bijanzadeh, H. R. *Synthesis* **2007**, 3056. (g) Adib, M.; Sheibani, E.; Abbasi, A.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2007**, *48*, 1179. (h) Adib, M.; Sheibani, E.; Mostofi, M.; G hanbary, K.; Bijanzadeh, H. R. *Tetrahedron* **2006**, *62*, 3435. (i) Adib, M.; Mahdavi, M.; Mahmoodi, N.; Pirelahi, H.; Bijanzadeh, H. R. *Synlett* **2006**, 1765.

(20) **General Procedure for the Preparation of Compounds 4a–l**

A mixture of *N*-isocyaniminotriphenylphosphorane (1 mmol) and the appropriate aldehyde (1 mmol) was dissolved in hot THF (5 mL). Then the appropriate 4 (3*H*)-quinazolinone (1 mmol) was added to the reaction mixture which was refluxed for 3 h. Then, the solvent was removed under the reduced pressure, and the residue was purified by TLC using $CHCl_3$–EtOAc (3:1) as eluent. The solvent was removed, and the product was obtained as colorless crystals.

3-[1-Hydroxy-1-(4-fluorophenyl)methyl]-5-phenyl-[1,2,4]triazolo[4,3-*c*]quinazoline (4c)

Yield 0.34 g (93%); colorless crystals; mp 192–193 °C. IR (KBr): 3266 (OH), 1609, 1515, 1374, 1332, 1264, 1211, 1187, 1156, 1106, 1056, 1019, 947, 863, 794, 769, 680 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 5.35 (br s, 1 H, CH), 6.02 (d, *J* = 4.6 Hz, 1 H, OH), 7.08 (dd, *J* = 8.8, 8.9 Hz, 2 H, 2 × CH), 7.11–7.19 (m, 2 H, 2 × CH), 7.56–7.66 (m, 4 H, 4 × CH), 7.78 (dd, *J* = 6.8, 7.4 Hz, 2 H, 2 × CH), 7.86 (dd, *J* = 7.3, 8.1 Hz, 1 H, CH), 7.96 (d, *J* = 8.1 Hz, 1 H, CH), 8.54 (d, *J* = 7.9 Hz, 1 H, CH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 65.94 (CH), 114.46 (d, $^2J_{FC}$ = 21.4 Hz, CH), 115.94 (C), 122.56, 127.89, 128.28 and 128.73 (4 × CH), 128.87 (d, $^3J_{FC}$ = 8.1 Hz, CH), 129.25, 130.63 and 131.83 (3 × CH), 133.48 (C), 137.16 (d, $^4J_{FC}$ = 2.7 Hz, C), 140.33, 145.65, 148.88 and 150.75 (4 × C), 161.45 (d, $^1J_{CF}$ = 243.2 Hz, CF). MS (EI): *m/z* (%) = 370 (6) [M^+], 279 (20), 247 (12), 205 (9), 167 (23), 149 (100), 113 (10), 104 (9), 83 (9), 71 (18), 57 (29). Anal. Calcd for $C_{22}H_{15}FN_4O$ (370.38): C, 71.34; H, 4.08; N, 15.13. Found: C, 71.3; H, 4.2; N, 15.1.

3-[1-Hydroxy-1-(4-nitrophenyl)methyl]-5-(4-methylphenyl)[1,2,4]triazolo[4,3-*c*]quinazoline (4f)

Yield 0.40 g (97%); colorless crystals; mp 228 °C. IR (KBr): 3344 (OH), 1614, 1511, 1466, 1335, 1181, 1105, 1069, 1039, 986, 948, 818, 769, 696 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 5.52 (d, *J* = 5.8 Hz, 1 H, CH), 6.25 (d, *J* = 5.8 Hz, 1 H, OH), 7.37 (d, *J* = 7.2 Hz, 2 H, 2 × CH), 7.49 (d, *J* = 8.7 Hz, 2 H, 2 × CH), 7.73 (d, *J* = 7.8 Hz, 2 H, 2 × CH), 7.79 (dd, *J* = 7.4, 7.7 Hz, 1 H, CH), 7.88 (t, *J* = 7.1, 7.2 Hz, 1 H, CH), 7.98 (d, *J* = 8.1 Hz, 1 H, CH), 8.16 (d, *J* = 8.7 Hz, 2 H, 2 × CH), 8.53 (d, *J* = 7.4 Hz, 1 H, CH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 21.12 (CH_3), 65.77 (CH), 115.83 (C), 122.61, 122.92, 127.93, 127.96, 128.75, 128.85, 129.26 (7 × CH), 130.59 (C), 131.98 (CH), 140.48, 140.52, 145.81, 146.79, 148.70, 149.08 and 150.11 (7 × C). MS (EI): *m/z* (%) = 411 (2) [M^+], 386 (5), 370 (14), 277 (100), 247 (31), 205 (24), 183 (19), 152 (16), 123 (12), 97 (18), 77 (28). Anal. Calcd for $C_{23}H_{17}N_5O_3$ (411.41): C, 67.15; H, 4.16; N, 17.02. Found: C, 67.2; H, 4.2; N, 16.9.

(21) Ugi, I. *Isonitrile Chemistry*; Academic Press: London, **1971**.

(22) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810.

(23) Walborsky, H. M.; Periasamy, M. P. In *The Chemistry of Functional Groups*, Suppl. C; Patai, S.; Rappaport, Z., Eds.; Wiley: New York, **1983**, Chap. 20, 835–837.