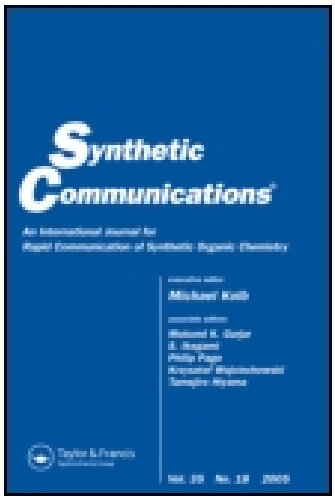


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# A REGIOSPECIFIC SYNTHESIS OF 1-HETEROCYCLIC SUBSTITUTED 1,2,4-TRIAZOLES VIA ADDITION REACTION OF 1,2,4-TRIAZOLE WITH FUNCTIONALIZED CARBODIIMIDE

Ming-Wu Ding [a] , Gui-Ping Zeng [a] & Zhao-Jie Liu [b]

[a] Institute of Organic Synthesis , Central China Normal University , Wuhan, 430079, P.R. China

[b] Institute of Organic Synthesis , Central China Normal University , Wuhan, 430079, P.R. China

Published online: 16 Aug 2006.

To cite this article: Ming-Wu Ding , Gui-Ping Zeng & Zhao-Jie Liu (2002) A REGIOSPECIFIC SYNTHESIS OF 1-HETEROCYCLIC SUBSTITUTED 1,2,4-TRIAZOLES VIA ADDITION REACTION OF 1,2,4-TRIAZOLE WITH FUNCTIONALIZED CARBODIIMIDE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:19, 3057-3062, DOI: 10.1081/SCC-120012998

To link to this article: http://dx.doi.org/10.1081/SCC-120012998

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016



SYNTHETIC COMMUNICATIONS
Vol. 32, No. 19, pp. 3057–3062, 2002



# A REGIOSPECIFIC SYNTHESIS OF 1-HETEROCYCLIC SUBSTITUTED 1,2,4-TRIAZOLES VIA ADDITION REACTION OF 1,2,4-TRIAZOLE WITH FUNCTIONALIZED CARBODIIMIDE

**Ming-Wu Ding, Gui-Ping Zeng, and Zhao-Jie Liu***

Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P.R. China

## ABSTRACT

The reaction of 1,2,4-triazole with functionalized carbodiimide **2** or **6** under solid $K_2CO_3$ provide a convenient and regiospecific route to 1-(2-imidazolonyl)-1,2,4-triazole **4** or 1-(2-quinazolonyl)-1,2,4-triazole **8**.

*Key Words:* Triazoles; Iminophosphorane; Imidazolinones; Quinazolinones; Aza-Wittig reaction

Many 1-substituted 1,2,4-triazole compounds show good fungicidal activities and plant growth regulative activities. They are generally prepared by N-alkylations of 1,2,4-triazole with alkylating reagents, of which various types have been used, however, many of these reactions

*Corresponding author. E-mail: ding5229@yahoo.com.cn



DOI: 10.1081/SCC-120012998 0039-7911 (Print); 1532-2432 (Online)

are limited by the simultaneous formation of the unwanted and biologically inactive 4-isomer.[1] It was reported that 1,2,4-triazole derivatives can be regiospecifically synthesized by addition reactions of 1,2,4-triazole with aldehydes and this method was successfully utilized to prepare many novel triazole derivatives.[2–5] However, there is no report about addition reaction of 1,2,4-triazole with carbodiimide. Recently we provided a facile synthesis of 2-substituted imidazolinones and quinazolinones via tandem aza-Wittig reaction.[6–8] We now report a new regiospecific synthesis of 2-heterocyclic substituted 1,2,4-triazoles via base catalytic addition reaction of 1,2,4-triazole with functionalized carbodiimide.

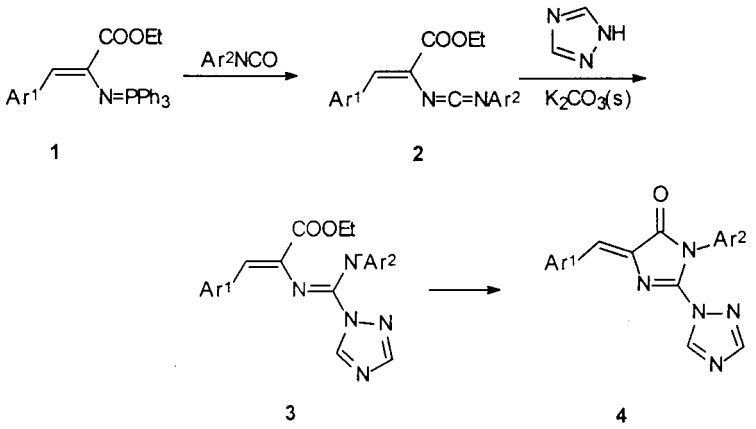
The easily accessible vinyliminophosphorane **1** reacted with aromatic isocyanates to give carbodiimides **2**. The direct reaction of **2** with 1,2,4-triazole at room temperature took place very slow for **2** did not disappear even after 5 days, however, when the reaction was carried out under solid $K_2CO_3$(s), the reaction mixture was getting red quickly and then becoming yellow gradually within 15 min. The final product obtained was verified to be 1-(2-imidazolonyl)-1,2,4-triazole **4**. No 4-isomer of **4** was formed during the reaction process. The structure of **4** has been characterized spectroscopically. For example, the $^1$H NMR spectrum data in **4a** showed the signals of 3-H in triazole ring at 7.94 ppm as a single absorption and 5-H at 8.97 ppm as a single absorption. The use of a 10-fold of excess solid $K_2CO_3$(s) gave better yields of **4**. The best reaction time was 15 min, for the reaction mixture was getting dark gradually after 15 min due to side reactions (Table 1). The formation of **4** can be rationalized in terms of an initial nucleophilic addition of 1,2,4-triazole under potassium carbonate to give the intermediate **3** which directly cyclized to give **4** (Sch. 1).

The above method was also successively applied to synthesize 1-(2-quinazolonyl)-1,2,4-triazole **8**, which having been found to show fungicidal activities.[9] Iminophosphorane **5** reacted with aromatic isocyanates to give carbodiimides **6**, which was allowed to react with 1,2,4-triazole under solid potassium carbonate to give **8** (Sch. 2). Good yields of **8** were obtained when catalytic solid potassium carbonate was used with overnight stirring (Table 1). The structure of **8** has been characterized spectroscopically. For example, the $^1$H NMR spectrum data in **8a** showed the signals of 3-H in triazole ring at 8.14 ppm as a single absorption and 5-H at 8.60 ppm as a single absorption. The formation of **8** can be rationalized in terms of an initial nucleophilic addition of 1,2,4-triazole under potassium carbonate to give the intermediate **7** which directly cyclized to give **8**.

*Table 1.* Preparation of 1-(2-Imidazolonyl)-1,2,4-triazole **4** and 1-(2-Quinazolonyl)-1,2,4-triazole **8**

| Compds. | $Ar^1$ | $Ar^2$ | Ar | Reaction Time (h) | $K_2CO_3$(s) | Yield (%)* |
|---|---|---|---|---|---|---|
| **4a** | Ph | Ph | | 0.25 | 10 equiv | 82 |
| | | | | 1 | 10 equiv | 38 |
| | | | | 24 | 10 equiv | 11 |
| | | | | 0.25 | 0.1 equiv | 22 |
| | | | | 0.25 | 1 equiv | 45 |
| **4b** | Ph | 4-Cl-Ph | | 0.25 | 10 equiv | 72 |
| **4c** | Ph | 3-Cl-Ph | | 0.25 | 10 equiv | 68 |
| **4d** | 4-Cl-Ph | 4-Cl-Ph | | 0.25 | 10 equiv | 87 |
| **4e** | 3-Cl-Ph | Ph | | 0.25 | 10 equiv | 80 |
| **4f** | 3-Cl-Ph | 4-Cl-Ph | | 0.25 | 10 equiv | 76 |
| **8a** | | | Ph | 24 | 0.1 equiv | 74 |
| **8b** | | | 4-Cl-Ph | 24 | 0.1 equiv | 70 |
| **8c** | | | 3-Cl-Ph | 24 | 0.1 equiv | 71 |

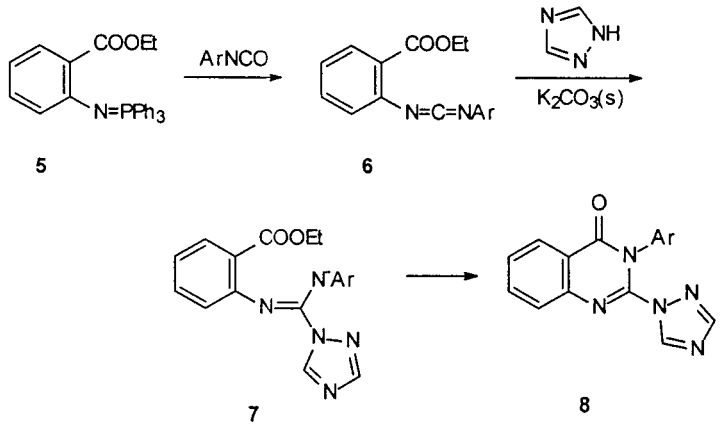
*isolated yields based on iminophosphoranes.




*Scheme 1.*

## EXPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a Shimadzu IR-408 infrared spectrometer. NMR were taken on a Varian XL-200 spectrometer.




*Scheme 2.*

### General Preparation of 1-(2-Imidazolonyl)-1,2,4-triazole 4

To a solution of vinyliminophosphorane **1** (5 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (5 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 4 ~ 6 h, the solvent was removed off under reduced pressure and ether/petroleum ether (1 : 2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was used directly without further purification. To the solution of **2** prepared above in $CH_3CN$ (15 mL) was added 1H-1,2,4-triazole (0.34 g, 5 mmol) and excess solid $K_2CO_3$ (6.9 g, 50 mmol). The mixture was stirred for 15 min vigorously at room temperature and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether or purified by a short silica gel column to give 1-(2-imidazolonyl)-1,2,4-triazole **4**.

**4a:** yellow crystals, m.p. 160 ~ 162°C, $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.97 (s, 1H, triazolyl-5-H), 7.94 (s, 1H, triazolyl-3-H), 8.21 ~ 7.18 (m, 11H, Ar–H and =CH); IR ($cm^{-1}$), 1722, 1640, 1560, 1476; MS (*m*/*z*), 315 ($M^+$, 100%), 171 (42%), 144 (14%), 117 (76%).

**4b:** yellow crystals, m.p. 197 ~ 199°C, $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 9.06 (s, 1H, triazolyl-5-H), 7.94 (s, 1H, triazolyl-3-H), 8.20 ~ 7.12 (m, 10H, Ar–H and =CH); IR ($cm^{-1}$), 1728, 1636, 1562, 1474; MS (*m*/*z*), 349 ($M^+$, 100%), 351 (33%), 205 (25%), 151 (40%), 116 (20%).

**4c:** yellow crystals, m.p. 152 ~ 154°C, $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 9.08 (s, 1H, triazolyl-5-H), 7.94 (s, 1H, triazolyl-3-H), 8.22 ~ 7.14

(m, 10H, Ar–H and =CH); IR ($cm^{-1}$), 1725, 1638, 1558, 1475; MS (*m*/*z*), 349 ($M^+$, 100%), 351 (34%), 205 (23%), 151 (28%), 116 (19%).

**4d:** yellow crystals, m.p. 197 ~ 199°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 9.10 (s, 1H, triazolyl-5-H), 7.90 (s, 1H, triazolyl-3-H), 8.20 ~ 7.10 (m, 9H, Ar–H and =CH); IR ($cm^{-1}$), 1730, 1638, 1550, 1478, MS (*m*/*z*), 383 ($M^+$, 100%), 385 (62%), 387 (11%), 205 (47%), 151 (30%).

**4e:** yellow crystals, m.p. 176 ~ 178°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 9.06 (s, 1H, triazolyl-5-H), 7.92 (s, 1H, triazolyl-3-H), 8.21 ~ 7.12 (m, 10H, Ar–H and =CH); IR ($cm^{-1}$), 1728, 1640, 1552, 1478; MS (*m*/*z*), 349 ($M^+$, 100%), 351 (33%), 205 (27%), 151 (36%).

**4f:** yellow crystals, m.p. 218 ~ 220°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 9.02 (s, 1H, triazolyl-5-H), 7.88 (s, 1H, triazolyl-3-H), 8.18 ~ 7.03 (m, 9H, Ar–H and =CH); IR ($cm^{-1}$), 1735, 1640, 1548, 1478; MS (*m*/*z*), 383 ($M^+$, 88%), 385 (61%), 387 (11%), 205 (58%), 151 (58%).

## General Preparation of 1-(2-Quinazolonyl)-1,2,4-triazole 8

To a solution of iminophosphorane **5** (2.12 g, 5 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (5 mmol) under nitrogen at 0 ~ 5°C. After the reaction mixture was stand for 6 ~ 12 h at 0 ~ 5°C, the solvent was removed off under reduced pressure and ether/petroleum ether (1 : 2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **6**, which was used directly without further purification. To the solution of **6** prepared above in $CH_3CN$ (15 mL) was added 1H-1,2,4-triazole (0.34 g, 5 mmol) and catalytic solid $K_2CO_3$ (0.07 g, 0.5 mmol). The mixture was stirred overnight at room temperature and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether or purified by a short silica gel column to give 1-(2-quinazolonyl)-1,2,4-triazole **8**.

**8a:** white crystals, m.p. 148 ~ 150°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 8.60 (s, 1H, triazolyl-5-H), 8.14 (s, 1H, triazolyl-3-H), 8.32 ~ 6.90 (m, 9H, Ar–H); IR ($cm^{-1}$), 1684, 1550, 1300; MS (*m*/*z*), 289 ($M^+$, 100%), 221 (46%), 144 (14%), 77 (66%).

**8b:** white crystals, m.p. 156 ~ 158°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 8.68 (s, 1H, triazolyl-5-H), 8.16 (s, 1H, triazolyl-3-H), 8.36 ~ 6.92 (m, 8H, Ar–H); IR ($cm^{-1}$), 1686, 1552, 1306; MS (*m*/*z*), 323 ($M^+$, 100%), 325 (32%), 255 (40%), 220 (12%), 144 (16%), 90 (71%).

**8c:** white crystals, m.p. 150 ~ 152°C, $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 8.66 (s, 1H, triazolyl-5-H), 8.16 (s, 1H, triazolyl-3-H), 8.35 ~ 6.90

(m, 8H, Ar–H); IR ($cm^{-1}$), 1685, 1550, 1302; MS (*m*/*z*), 323 ($M^+$, 100%), 325 (33%), 255 (48%), 144 (24%), 90 (56%).

## ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (Project No. 20102001).

## REFERENCES

1. Bentley, T.W.; Jones, R.V.H.; Wareham, P. J. Tetrahedron Lett. **1989**, *30*, 4013.
2. Smith, K.; Hammond, M.E.W.; James, D.M.; Ellison, I.J.; Hutchings, Chem. Lett. **1990**, 351.
3. Smith, K.; Small, A.; Hutchings, M.G. Synlett. **1991**, 485.
4. Seele, R.; Goetz, N.; Brox, W.; Kober, R.; Ammermann, E.; Lorenz, G. EP449067 (1991).
5. Seele, R.; Goetz, N.; Saupe, T.; Lorenz, G.; Ammermann, E. Ger. Offen. 4034352 (1992).
6. Ding, M.W.; Zeng, G.P.; Wu, T. J. Synth. Commun. **2000**, *30*, 1599.
7. Ding, M.W.; Xu, Z.F.; Wu, T. J. Synth. Commun. **1999**, *29*, 1171.
8. Ding, M.W.; Tu, H.Y.; Liu, Z. J. Synth. Commun. **1997**, *27*, 3657.
9. Green, D.E.; Percival, A. EP183458 (1986).

Received in the Netherlands September 21, 2001