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PASE synthesis of 1-azolyl-1*H*-1,2,4-triazoles by the reaction of diazoazoles with ethyl isocyanoacetate

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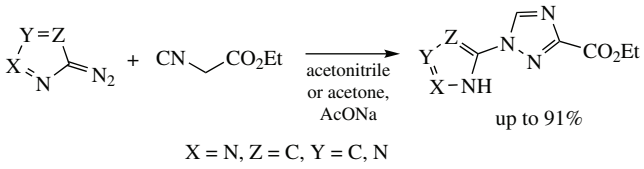
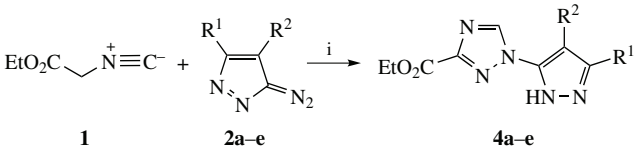
PASE (pot, atom and step economic) synthesis of 1-azolyl-1*H*-1,2,4-triazole derivatives in up to 91% yield has been accomplished by addition of 5-diazoazoles to ethyl isocyanoacetate.



Among heterocyclic compounds, five-membered nitrogen ones are the most important as they represent a key structural part of many natural products and modern drugs.[1–3] Triazole derivatives attract a lot of attention in the field of drug design,[4–7] agrochemistry[8] and materials science.[9–11] Many triazole derived drugs such as Fluconazole, Itraconazole, Posaconazole, Voriconasole, Ravuconazole (antifungal), Ribavirin (antiviral), Rizatriptan (migraine headaches), Trapidil (hypotensive), Trazodon, Etoperidone, Nefazodone (antidepressants), Vorozole, Anastrozole, Letrozole (antineoplastics), Rilmazafone (sedative, hypnotic), Etizolam (anticonvulsant) are currently on the market. Various products containing the 1,2,4-triazole nucleus, *e.g.*, Tebuconazole, Epoxiconazole, Difenoconazole (fungicides), Diniconazole, Triazophose (pesticides), Amitrole, Epronaz, Flupoxam (herbicides) and Paclobutrazole, Diclobutrazole (plant growth regulators) find agricultural applications.

Numerous methods are available to obtain N-substituted 1,2,4-triazoles.[12–15] However, some of them have restrictions. For example, direct alkylation of 1,2,4-triazole usually affords a mixture of isomeric products. This difficulty can in principle be circumvented by introduction of an alkyl group before ring closure, however few convenient routes are known. Coupling of aryldiazonium salts with methyl isocyanoacetate[16,17] or tosylmethyl isocyanide[18] is an efficient approach to produce 1-aryl-1,2,4-triazoles. However, the heterocyclization takes place only for electron rich diazonium salts, otherwise arenecarboxamides are formed.[16] Recently flow modification to construct triazoles by the reaction of diazonium salts with isocyanoacetate[19] as well as silver or copper catalyzed cycloadditions have been published.[20] Meanwhile, no examples of participation of heterocyclic diazo compounds possessing specific reactivivty[21] in such a cycloaddition can be found.



1 **2a–e** **4a–e**

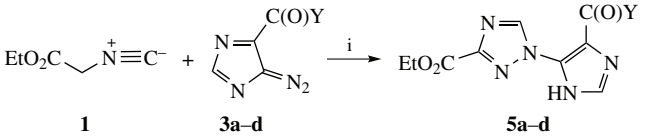
a R^1 = Ph, R^2 = H, 74%
b R^1 = 4-MeC_6H_4, R^2 = H, 81%
c R^1 = 4-$MeOC_6H_4$, R^2 = H, 80%
d R^1 = 4-ClC_6H_4, R^2 = H, 82%
e R^1 = H, R^2 = CO_2Et, 90%

Scheme 1 *Reagents and conditions*: i, acetonitrile, AcONa.

In the present work, we investigated the reaction of ethyl isocyanoacetate **1** with 5-diazopyrazoles **2a–g** (Scheme 1) and 5-diazoimidazoles **3a–d** (Scheme 2). It is well known that the coupling of 5-diazoazoles or relative diazonium salts with CH-acids leads to the corresponding azol-5-ylhydrazones.[22,23] Depending on the nature of the reactants and on the medium pH value, these coupling products can either be isolated or be directly cyclized to azolo[5,1-*c*][1,2,4]triazine or azolo[5,1-*c*]-[1,2,4]triazin-4-one derivatives.[24,25]

Coupling of ethyl isocyanoacetate **1** with 5-diazopyrazoles **2a–e** and 5-diazoimidazoles **3a–d** was performed in acetonitrile or acetone in the presence of sodium acetate. To our delight, the expected triazoles **4a–e** and **5a–d** were isolated in up to 91% yield.†

The structure of compounds **4a–e** and **5a–d** was confirmed unambiguously by spectral data. The ^{1}H NMR spectra of triazole

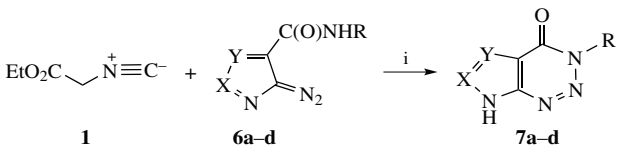


1 **3a–d** **5a–d**

a Y = OEt, 83%
b Y = pyrrolidin-1-yl, 75%
c Y = piperidin-1-yl, 78%
d Y = morpholin-4-yl, 91%

Scheme 2 *Reagents and conditions*: i, acetone, AcONa.

† *General procedure for the synthesis of* **4a–e** *and* **5a–d**. To a stirred mixture of ethyl isocyanoacetate **1** (60 μl, 0.55 mmol)[26] and sodium acetate (45 mg, 0.55 mmol) in acetonitrile (3 ml) or acetone (3 ml), a cold solution of the corresponding 5-diazopyrazole **2a–e** (0.5 mmol)[27,28] in acetonitrile (3 ml) or 5-diazoimidazole **3a–d** (0.5 mmol)[29,30] in acetone (3 ml) was added dropwise at 0 °C for 5 min. The temperature of the mixture was raised to ambient, and the mixture was left until disappearing of the starting diazoazole (3–4 days, TLC control). Activated charcoal was added, the mixture was stirred for 15 min and filtered. The filtrate



a X = N,Y = CH, R = H, 88% **c** X = CH,Y = N, R = H, 83%
b X = N,Y = CH, R = Me, 85% **d** X = CH,Y = N, R = Me, 90%

Scheme 3 *Reagents and conditions*: i, acetone, AcONa.

part of these compounds revealed signals for CO_2Et fragment at δ 1.41–1.46 and 4.38–4.49 ppm, respectively, as well as singlet of H(5) triazole ring at δ 8.71–9.04 ppm. The ^{13}C NMR spectra contain triazole signals at 142.3–148.6 ppm for C(5) and 154.2–155.8 ppm for C(3).

However, the reaction has some restrictions. The use of 5-diazoazoles **6a–d** containing 4-positioned NH-amide groups afforded products of alternative transformation, *viz*., azolo[4,5-*d*][1,2,3]triazin-4(3*H*)-ones **7a–d**‡ (Scheme 3).

In conclusion, it was demonstrated that the reaction of 5-diazoazoles with ethyl isocyanoacetate is an efficient PASE approach to the corresponding 1-azolyl-1*H*-1,2,4-triazole derivatives. The reaction scope is rather broad. The prepared hybrid heterocyclic compounds look highly attractive as interesting ligands for coordination chemistry as well as precursors for metal-organic frameworks (MOF) synthesis.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.016.

References

1 A. Ansari, A. Ali, M. Asif and Shamsuzzaman, *New J. Chem.*, 2017, **41**, 16.
2 L. D. Luca, *Curr. Med. Chem*., 2006, **13**, 1.
3 I. A. Al-Masoudi, Y. A. Al-Soud, N. J. Al-Salihi and N. A. Al-Masoudi, *Chem. Heterocycl. Compd*., 2006, **42**, 1377 (*Khim. Geterotsikl. Soedin.*, 2006, 1605).
4 S. S. Kumar and H. P. Kavitha, *Mini-Rev. Org. Chem.*, 2013, **10**, 40.
5 S. Maddila, R. Pagadala and S. B. Jonnalagadda, *Lett. Org. Chem.*, 2013, **10**, 693.
6 F. Ahmadi, M. R. Ghayahbashi, M. Sharifzadeh, E. Alipoiur, S. N. Ostad, M. Vosooghi, H. Reza Khademi and M. Amini, *Med. Chem.*, 2015, **11**, 69.
7 Ş. G. Küçükgüzel and P. Çıkla-Süzgün, *Eur. J. Med. Chem*., 2015, **97**, 830.
8 K. Shalini, N. Kumar, S. Drabu and P. K. Sharma, *Beilstein J. Org. Chem*., 2011, **7**, 668.
9 V. N. Bulut, C. Duran, A. Gundogdu, M. Soylak, N. Yildirim and M. Tufekci, *Bull. Chem. Soc. Ethiop*., 2010, **24**, 457.
10 A. Diaz-Ortiz, P. Prieto, J. R. Carrillo, R. Martin and I. Torres, *Curr. Org. Chem.*, 2015, **19**, 568.
11 G. Aromi, L. A. Barrios, O. Roubeau and P. Gamez, *Coord. Chem. Rev.*, 2011, **255**, 485.
12 M. Balasubramanian, J. G. Keay, E. F. V. Scriven and N. Shobana, *Heterocycles*, 1994, **37**, 1951.
13 A. Moulin, M. Bibian, A.-L. Blayo, S. El Habnouni, J. Martinez and J.-A. Fehrentz, *Chem. Rev*., 2010, **110**, 1809.
14 S. C. Holm and B. F. Straub, *Org. Prep. Proced. Int.*, 2011, **43**, 319.
15 P. Kaur, R. Kaur and M. Goswami, *Int. Res. J. Pharm.*, 2018, **9** (7), 1.
16 K. Matsumoto, M. Suzuki, M. Tomie, N. Yoneda and M. Miyoshi, *Synthesis*, 1975, **9**, 609.
17 A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru and V. G. Nenajdenko, *Chem. Rev*., 2010, **110**, 5235.
18 A. M. van Leusen, B. E. Hoogenboom and H. A. Houwing, *J. Org. Chem*., 1976, **41**, 711.
19 M. Baumann, A. M. R. Garcia and I. R. Baxendale, *Org. Biomol. Chem*., 2015, **14**, 4231.
20 J.-Q. Liu, X. Shen, Y. Wang, X.-S. Wang and X. Bi, *Org. Lett*., 2018, **20**, 6930.
21 V. S. Mokrushin and E. V. Sadchikova, *Khimiya geterotsiklicheskikh diazosoedinenii (Chemistry of Heterocyclic Diazo Compounds)*, Prospekt nauki, St. Petersburg, 2013 (in Russian).
22 M. A. Bezmaternykh, V. S. Mokrushin, T. A. Pospelova and O. S. Eltsov, *Chem. Heterocycl. Compd.,* 1998, **34**, 702 (*Khim. Geterotsikl. Soedin.*, 1998, 805).
23 E. V. Shchegol'kov, E. V. Sadchikova, Ya. V. Burgart and V. I. Saloutin, *Russ. Chem. Bull., Int. Ed.,* 2008, **57**, 612 (*Izv. Akad. Nauk, Ser. Khim*., 2008, 599).
24 E. V. Sadchikova and V. S. Mokrushin, *Chem. Heterocycl. Compd*., 2014, **50**, 1014 (*Khim. Geterotsikl. Soedin.*, 2014, 1100).
25 E. V. Shchegol'kov, E. V. Sadchikova, Ya. V. Burgart and V. I. Saloutin, *Russ. J. Org. Chem*., 2009, **45**, 572 (*Zh. Org. Khim*., 2009, **45**, 586).
26 R. Obrecht, R. Herrmann and I. Ugi, *Synthesis*, 1985, 400.
27 D. L. Alekseeva, V. Yu. Rakhimova, A. S. Minin, A. V. Belousova and E. V. Sadchikova, *Chem. Heterocycl. Compd*., 2018, **54**, 1145 (*Khim. Geterotsikl. Soedin.*, 2018, 1145).
28 Y. F. Shealy and C. A. O'Dell, *J. Pharm. Sci*., 1971, **60**, 554.
29 K. E. Andersen and E. B. Pedersen, *Liebigs Ann. Chem*., 1986, 1012.
30 E. V. Sadchikova and V. S. Mokrushin, *Russ. Chem. Bull.*, *Int. Ed*., 2003, **52**, 1600 (*Izv. Akad. Nauk*, *Ser. Khim.*, 2003, 1516).
31 C. C. Cheng, R. K. Robins, K. C. Cheng and D. C. Lin, *J. Pharm. Sci.*, 1968, **57**, 1044.
32 M. F. G. Stevens, *Prog. Med. Chem.*, 1976, **13**, 205.
33 Y. F. Shealy, R. F. Struck, L. B. Holum and J. A. Montgomery, *J. Org. Chem.*, 1961, **26**, 2396.

was concentrated under reduced pressure at a temperature below 40 °C. The residue was treated with diethyl ether or hexane, the precipitate formed was collected by filtration and purified by flash column chromatography on silica gel (eluting with EtOAc–CH_2Cl_2 mixture).

‡ *General procedure for the synthesis of* **7a–d**. To a stirred mixture of ethyl isocyanoacetate **1** (60 μl, 0.55 mmol) and sodium acetate (45 mg, 0.55 mmol) in acetone (3 ml), a cold solution of the corresponding 5-diazoazole **6a–d** (0.5 mmol)[28–30] in acetone (3 ml) was added dropwise at 0 °C for 5 min. The mixture was left until disappearing of the starting diazoazoles (TLC control). Activated charcoal was added, and the mixture was stirred for 15 min and filtered. The filtrate was concentrated under reduced pressure at a temperature below 40 °C. The residue was crystallized from EtOH as white solid. Yield 60 mg (88%) for **7a**,[31,32] 64 mg (85%) for **7b**,[32] 57 mg (83%) for **7c**,[30,33] 68 mg (90%) for **7d**.[30] Physical and spectral characteristics of these compounds are identical to the reported ones.[30–33]

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