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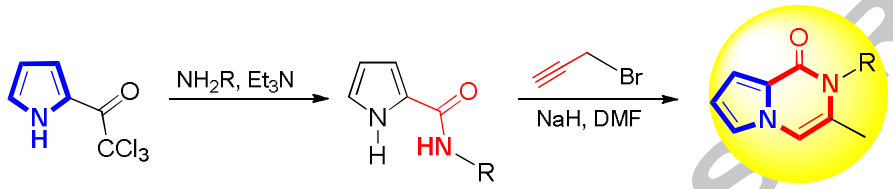

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Selective synthesis of *N*-substituted pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one derivatives via alkyne cyclization

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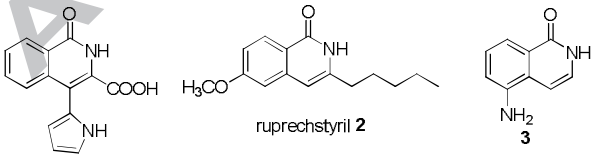
ABSTRACT

A novel and efficient synthesis of N-substituted pyrrolo-pyrazinone derivatives has been developed. A trichloroacetyl group connected to the pyrrole ring was converted into the desired carboxamide derivatives. Promoted by NaH, the pyrrole carboxamide derivatives underwent a tandem reaction with propargyl bromide to afford pyrrolo-pyrazinones with high efficiency under very mild conditions. The mechanism for the formation of the products is discussed and supported by DFT calculations.

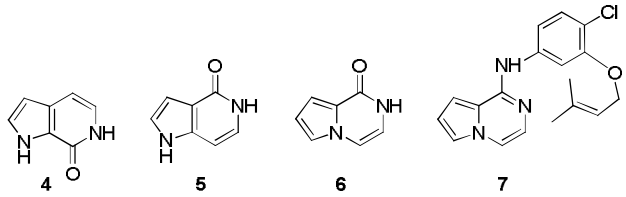
Isoquinolines are found in several bioactive natural products and they are an important family of alkaloids with key biological activities in the central nervous system.[1] The isoquinolinone scaffold[2] has been used as a basic building block for the synthesis of various isoquinolinone ring systems.[3] Some isoquinolinone derivatives exhibit important biological effects such as antitumor, antibiotic and cardiovascular activities.[3] For example, marinamide (**1**) is a novel isoquinolinone derivative that exhibits significant antitumor activitiy.[4] Ruprechstyril (**2**), having an isoquinolinone structure, is a natural product isolated from *Ruprechtia tangarana*; a bioassay showed that **2** had anticancer activity.[5] More recently, Threadgill *et al.* reported the synthesis of a series of amino-isoquinolinone derivatives **3** substituted at the amine group, which demonstrated selective inhibition of PARP-2.[6]



More importantly, the range of the activity did not change when the benzene ring in **1-3** was replaced by other heterocycles such as furan, thiophene, and pyrrole rings.

Annulation of a pyrrole ring next to the carbonyl group of a pyridin-2(1*H*)-one ring results in the formation of two regioisomeric pyrrolo-pyridinones **4** and **5**. The isomer **4** and several derivatives are suitable as inhibitors of purine nucleoside phosphorylase (PNP).[7]

The regioisomeric compound **5** has been used as the key compound in the synthesis of pyrrolo[1,2-*a*]pyrazine systems, which were found to have significant activity in the blockade of apomorphine stereotype and apomorphine-induced climbing.[8]



Incorporation of the nitrogen atom of pyrrole into pyridin-2(1*H*)-one gave compound **6**. There is only one reference in the literature[9] for the synthesis of this compound starting from 1*H*-pyrrole-2-carbonitrile. The procedure published by Romero *et al.*[10] was successfully applied to the synthesis of pyrrolo-pyrazine derivative **7**, which is a non-nucleoside inhibitor of HIV-1 reverse transcriptase.

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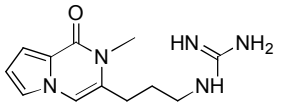
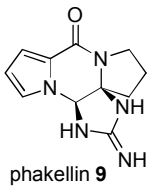


peramine **8**

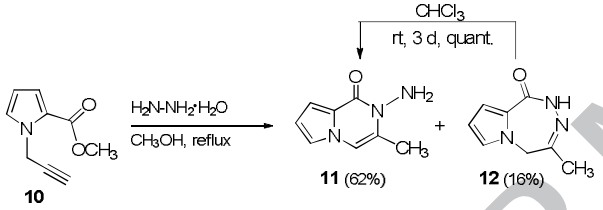


phakellin **9**

The alkaloid peramine (**8**)[11] containing a pyrrolo-pyrazinone skeleton with a guanidino group was isolated from perennial rye grass and is an insect feeding deterrent.[12] On the other hand, the imidazole-condensed dihydropyrrolo-pyrazine derivative phakellin (**9**) belongs to the family of marine sponge derived alkaloids[13] and it has attracted significant interest from both synthetic and biological perspectives because of its intriguing structural and potent biological activities.[14]

Because of the structural diversity of compound **6**, we herein describe a methodology for the synthesis of pyrrolo-pyrazinone derivatives substituted at the N-atom via alkyne cyclization.

In our previous studies, we synthesized triazepinone derivative **12** by an intramolecular ring cyclization reaction of a propargyl ester **10** with hydrazine monohydrate.[15] The expected product **12** was formed in 16% yield. Furthermore, triazepinone derivative **12** was smoothly rearranged into the six-membered ring isomer **11** in quantitative yield. Calculations showed that the isomer **11** was 4.28 kcal/mol more stable than the isomer **12** (Scheme 1).



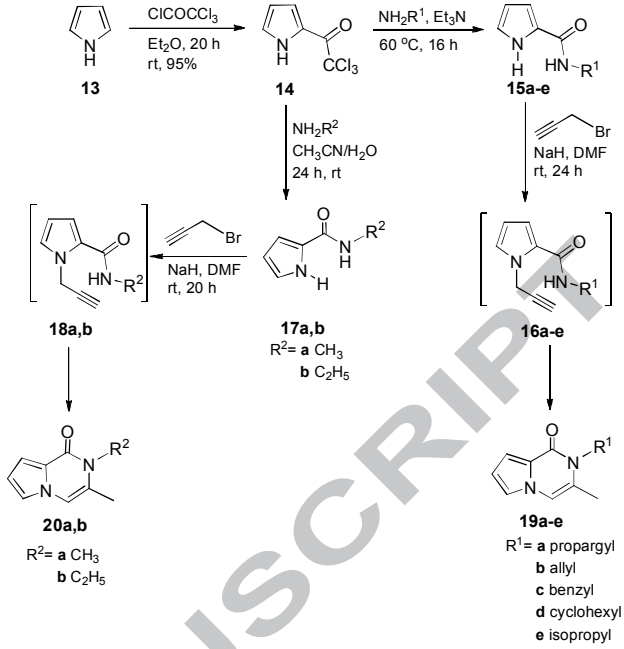
Scheme 1. Reaction of **10** with hydrazine

On the basis of this experience, we decided to investigate the reaction of **14** possessing a better leaving group, i.e., -CCl_3, with substituted amines and to develop a general methodology for the synthesis of pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones substituted at the N-atom. The synthesis of the key compound **14** was accomplished via a slightly modified route, as previously reported, in high yield starting from pyrrole.[16] The acetylation of pyrrole (**13**) with trichloroacetyl chloride gave 2-(trichloroacetyl)pyrrole (**14**) in 95% yield.

Next, the reaction of **14** with various primary amines in the presence of triethylamine gave the corresponding amides **15a-e**[17-21] in 76-88% yields (Scheme 2). However, the reaction with methylamine and ethylamine did not proceed as well as in the case of the other amines. The reactions with methylamine and ethylamine were instead carried out in acetonitrile to give the amides **17a**[22] and **17b**[21] in yields of 76% and 91%, respectively.

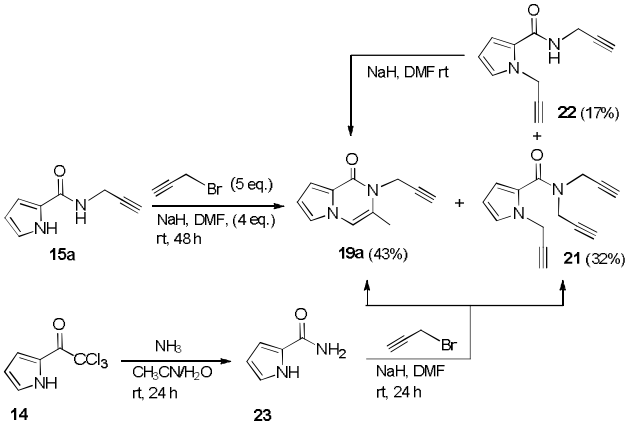
Treatment of the synthesized pyrrole-2-carboxamides **15** and **17** with NaH in DMF followed by addition of propargyl bromide did not lead to the expected propargyl substituted pyrrolecarboxamides **16** and **18**. But fortunately, the desired cyclization products, pyrrolo-pyrazinone derivatives **19** and **20**, were formed by a domino reaction.

We also examined the reaction of **15a** with excess propargyl bromide in the presence of NaH. The reaction was carried out under the same conditions in DMF at room temperature. Besides the expected ring-closure product **19a**, we isolated two additional products, **21** and **22**; the yields were 43%, 32% and 17%, respectively (Scheme 3 and Table 1).



Scheme 2. Synthesis of pyrrolopyrazinone derivatives **19a-e** and **20a,b**.

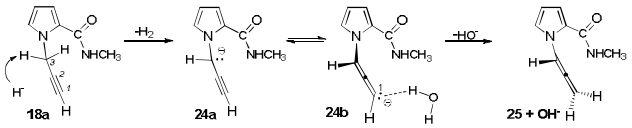
Treatment of **22** with NaH in DMF under the same reaction conditions resulted in the formation of the ring-closed product **19a**. Unfortunately, an allene having the structure **25** (see Scheme 4 and Table 1) was not found among the products. We assume that the allene formed as an intermediate is highly reactive such that it immediately undergoes a cyclization reaction. The formation of **22** (17% yield) is attributed to the consumption of NaH in the reaction mixture. Furthermore, the isolation of this product shows that **22** cannot undergo a spontaneous cyclization reaction. For cyclization, either the NH proton must be abstracted or the alkyne must undergo isomerization into the allene. Furthermore, the reaction of the amide **23**,[23] synthesized by the reaction of **14** with NH_3, with propargyl bromide and NaH also gave the cyclization products **19a** (52%) and **21** (32%).[24]



Scheme 3. Reaction of **15a** with excess propargyl bromide.

A tentative mechanism for the formation of compounds **19** and **20** is outlined in Schemes 4 and 5. It is proposed that the first step is the formation of allene **25**. We assume that the nitrogen atom of the carboxyamide or an anion cannot attack the triple bond because of the increased electron density. However, the terminal alkyne **18a** can undergo a base-induced isomerization to give the terminal allene **25**.

Formation of pyrrolo-pyrazinone derivative **20a**[25] was investigated computationally in an effort to clarify the mechanism. First we calculated the heat of formation energies of the alkyne **18a** and the corresponding allene **25**, and found that the allene was about 2.8 kcal/mol (in DMF) more stable than the propargyl isomer **18a**. The geometrical parameters of the reactants, intermediates, transition states (TS) and products were fully optimized with the hybrid density functional B3LYP[26,27] method using the 6-31+G(d,p) basis set implemented in Gaussian 09,[28] for all structures.



Scheme 4. Mechanism for the isomerization of **18a** into **25**.

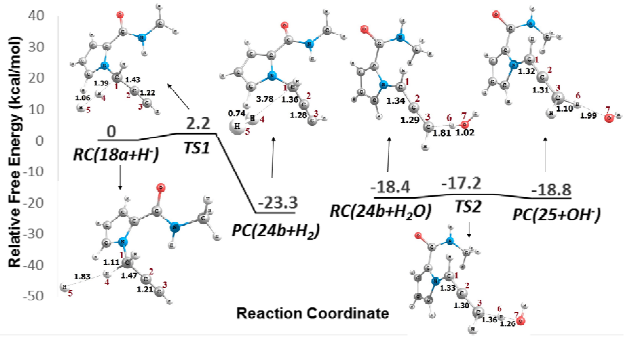
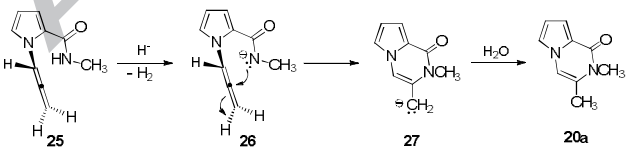


Figure 1. Potential energy profile related to propargyl-allene isomerization

We first modeled propargyl-allene isomerization from **18a** into **25** as shown in Scheme 4. We propose a mechanism that includes the abstraction of a proton with a hydride ion from an sp^3-hybridized carbon atom to form a complex between **24** and H_2O present in DMF. In the second step, the carbanion **24b** abstracts a proton from H_2O to generate the corresponding allene **25**. The small activation energies in Figure 1 (TS1) strongly support that cyclization takes place through allene intermediate **25**. After the formation of allene **25**, the reaction proceeds with nucleophilic attack of the nitrogen atom in **26** on the central carbon atom of the allene moiety (Scheme 5). The central carbon atom of an allene unit resonates at about 195-215 ppm, whereas terminal sp^2-carbon atoms appear at about 90 ppm. This large chemical shift difference shows the electropositive character of the central carbon atom in allenes. Therefore, the nucleophilic nitrogen atom can attack this central carbon atom and form the products. The activation barrier for this cyclization process was found to be 6.3 kcal/mol (TS3) (Figure 2). The next step is the proton transfer to give **27**. This step was modeled with the assistance of H_2O, which is present in the reaction medium.



Scheme 5. Mechanism for the cyclization of **25** into **20a**.

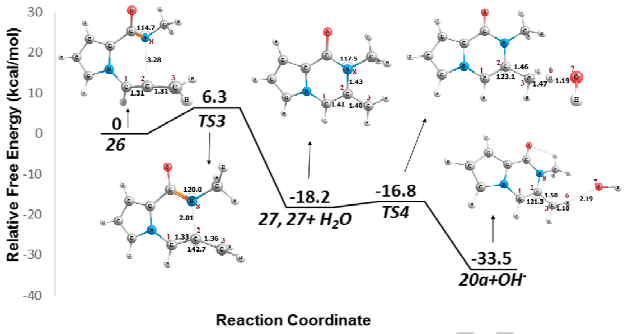
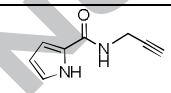
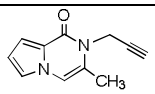
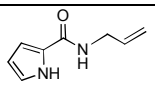
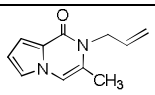
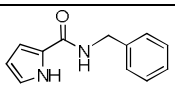
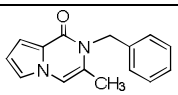
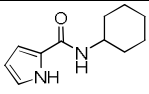
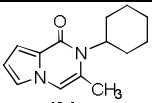
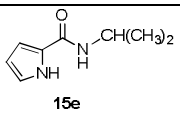
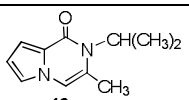
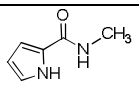
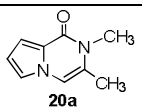
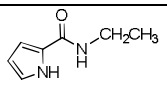
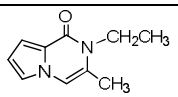


Figure 2. Potential energy profile for the cyclization of **25** into **20a**.

In conclusion we have established a highly selective, convenient and practical method to access N-substituted pyrrolo-pyrazinone derivatives in high yields and in three steps starting from pyrrole by alkyne cyclization in a simple reaction sequence. We assume that the methods developed herein will find frequent applications in heterocyclic chemistry and related areas.

Table 1. Reactions of pyrrole-carboxamides with propargyl bromide

Entry	Pyrrole-2-carboxamide	Pyrrolo-pyrazinone	Yield (%)
1	 **15a**	 **19a**	77
2	 **15b**	 **19b**	84
3	 **15c**	 **19c**	70
4	 **15d**	 **19d**	88
5	 **15e**	 **19e**	76
6	 **17a**	 **20a**	76
7	 **17b**	 **20b**	82

Acknowledgements

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Supplementary data

Supplementary data [experimental conditions, spectroscopic data (^{1}H and ^{13}C NMR spectra), and tables of atom coordinates and absolute energies of the calculated compounds associated with this article can be found, in the online version, at …..

References and notes

1. (a) Alvarez, M.; Joule, J. A. Isoquinolines, *Science of Synthesis* **2005**, *15*, 839-906 (b) Shamma, M. The Isoquinoline Alkaloids. *Chemistry and Pharmacology*; Academic Press: New York, **1972**.
2. Müjde, B.; Ozcan, S.; Balci, M. *Phytochem. Lett.* **2011**, 4, 407-410.
3. (a) Wischang, D.; Hartung, J. *Tetrahedron* **2011**, *67,* 4048-4054. (b) Chiarugi, A.; Meli, E.; Calvani, R.; Baronti, R.; Camaioni, E.; Constantino, G.; Marinozzi, M.; Giampietro, D. E. P.; Pellicciari, R.; Moroni, F. *J. Pharmacol. Exp. Thr.* **2003**, *305,* 943-949. (c) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. *J. Med. Chem.* **1996**, *39,* 4583. (d) Fidalgo, M. L.; Arias, M. S.; Soliveri, J.; Aries, M. E. *J. Antibiot.* **1992**, *45,* 1759.
4. (a) Zhu, F.; Chen, G. Y.; Wu, J. S.; Pan, J. H. *Nat. Prod. Res.* **2013**, *27*, 1960-1964. (b) Zhang, S.; Feng, C.; Jai, C.; Chen, J.; Ji, M. *J. Chem. Res.* **2013**, 291-293.
5. (a) Pettit, G. R.; Meng, Y.; Herald, D. L.; Graham, K. N. A.; Pettit, R. K.; Doubek, D. L. *J. Nat. Prod.* **2003**, *66,* 1065-1069. (b) Saeed, A. *Nat. Prod. Res.* **2013**, *27,* 1153-1158.
6. Sunderland, P. T.; Woon, E. C. Y.; Dhami, A.; Bergin, A. B.; Mahon, M. F.; Wood, P. J.; Jones, L. A.; Tully, S. R.; Lloyd, M. D.; Thompson, A. S.; Jawaid, H.; Martin, N. M. B. Threadgill, M. D. *J. Med. Chem.* **2011**, *54,* 2049-2059.
7. Morris, P. E.; Montgomery, J. A.; Babu, Y. S. U.S. Pat. Appl. Publ., 20010053784; **2001**; *Chem Abstr.*: **2001**, *136*, 37906.
8. New, J. S.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, R. F. Jr.; Vandermaelen, C. P.; Cipollina, J. A. *J. Med. Chem.* **1989**, *32,* 1147-1156.
9. Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**, *128,* 15372-15373.
10. For the synthesis of chloropyrrolopyrazines, see: Romero, R. S.; Franco, F.; Castaneda, A. C.; Muchowski, J. M., J. M. US 5041442 A 19910820; **1991**; *Chem Abstr.*: **1991**, *115*, 232289
11. Brimble, M. A.; Rowan, D. D. *J. Chem. Soc., Chem. Commun.* **1986**, 935.
12. Rowan, D. D.; Hunt, M. B. Gaynor, D. L. *J. Chem. Soc., Chem. Commun.* **1988**, 978-979.
13. Sharma, G. M.; Burkholder, P. R. *J. Chem. Soc., Chem. Commun.* **1971**, 151–152.
14. Wang, S.; Romo, D. *Angew. Chem. Int. Ed.* **2008**, *47,* 1284-1286.
15. Menges, N.; Sari, O.; Abdullayev, Y.; Erdem, S. S.; Balci, M. *J. Org. Chem.* **2013**, *78,* 5184-5195.
16. (a) Hewlett, N. M.; Tepe, J. J. *Org. Lett.* **2011**, *13,* 4550-4553. (b) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51,* 100-102.
17. (a) La Regina, G.; Silvestri, R.; Artico, M.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. *J. Med. Chem.* **2007**, *50,* 922-931. (b) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73,* 4746-4749.
18. Shafi, S.; Kedziorek, M.; Grela, K. *Synlett* **2011**, 124-128.
19. (a) Dyson, L.; Wright, A. D.; Young, K. A.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem.* **2014**, *22,* 1690-1699. (b) Huang, A.; Liu, F.; Zhan, C.; Liu, Y.; Ma, C. *Org. Bioorg. Chem.* **2011**, *9,* 7351-7357.
20. Thoi, V. S.; Stork, J. R.; Niles, E. T.; Depperman, E. C.; Tierney, D. L.; Cohen, S. M. *Inorg. Chem.* **2008**, *47,* 10533-10541.
21. (a) Huang, A.; Qiao, Z.; Zhang, X.; Yu, W.; Zheng, Q.; Ma, Y.; Ma, C. *Tetrahedron* **2012**, *68,* 906-912. (b) Huang, A.; Liu, F.; Zhan, C.; Liu, Y.; Ma, C. *Org. Biomol. Chem.* **2011**, *9*, 7351-7357.
22. (a) Tutino, F.; Papeo, G.; Quartieri, F. *J. Heterocycl. Chem.* **2010**, *56,* 112-117. (b) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965-75.
23. Troegel, B.;Lindel, T. *Org. Lett.* **2012**, *14,* 468-471.
24. Selected ^{1}H and ^{13}C NMR data:
    3-Methyl-2-(prop-2-ynyl)pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (19a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.06 (m, 1H), 7.01 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.82 (s, 1H), 6.51 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.79 (d, *J* = 2.5 Hz, 2H), 2.37 (d, *J* = 1.2 Hz, 3H), 2.24 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.0 (C=O), 124.0, 122.7, 117.8, 112.2, 110.6, 106.5, 78.9 (alkyne), 71.8 (alkyne), 31.25 (CH_2), 16.7 (CH_3).
    2,3-Dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20a).^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.05 (br d, *J* = 4.0 Hz, 1H), 7.00 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.82 (br s, 1H), 6.51 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.45 (s, 3H), 2.22 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.00 (C=O), 124.8, 123.1, 117.2, 112.0, 109.6, 105.9, 29.2 (NCH_3), 17.42 (CH_3).
    ***N*,*N*,1-Tri(prop-2-ynyl)-1*H*-pyrrole-2-carboxamide (21)**.^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.05 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.80 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.17 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.01 (d, *J* = 2.5 Hz, 2H), 4.44 (d, *J* = 2.1 Hz, 4H), 2.39 (t, *J* = 2.5 Hz, 1H), 2.32 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.02 (C=O) 126.1, 123.3, 114.6, 107.9, 78.6, 78.5, 73.5, 72.6, 37.8 (2C).
    ***N*-1-Di(prop-2-ynyl)-1*H*-pyrrole-2-carboxamide (22)**. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.09 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.61 (dd, *J* = 3.8, 1.5 Hz, 1H), 6.17 (dd, *J* = 3.8, 2.6 Hz, 1H), 6.01 (br s, 1H), 5.24 (d, *J* = 2.5 Hz, 2H), 4.18 (dd, *J* = 5.3, 2.5 Hz, 2H), 2.42 (t, *J* = 2.5 Hz, 1H), 2.26 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.1 (C=O), 126.7, 124.2, 112.8, 108.1, 79.7, 78.5, 73.6, 71.6, 38.1, 29.0.
25. Dumas, D. J. *J. Org. Chem.* **1988**, *53,* 4650-4653.
26. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.
27. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789.
28. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani G.; Barone, V.; Mennucci, B.; Cossi, Petersson, G. A.; Nakatsuji, H.; Caricato M.;, Li X.; Hratchian H.P.; Izmaylov A.F.; Bloino J.; Zheng G.; Sonnenberg J.L.; Hada M.; Ehara M.; Toyota K.; Fukuda R.; Hasegawa J.; Ishida M.; Nakajima T.; Honda Y.; Kitao O.; Nakai H.; Vreven T.; Montgomery J.A.; Jr.; Peralta J.E.; Ogliaro F.; Bearpark M.; Heyd J.J.; Brothers E.; Kudin K.N.; Staroverov V.N.; Keith T.; Kobayashi R.; Normand J.; Raghavachari K.; Rendell A.; Burant J.C.; Iyengar S.S.; Tomasi T.; Cossi M.; Rega N.; Millam J.M.; Klene M.; Knox J.E.; Cross J.B.; Bakken V.; Adamo C.; Jaramillo J.; Gomperts R.; Stratmann,R.E.; Yazyev O.; Austin A.J.; Cammi R.; Pomelli C.; Ochterski J.W.; Martin R.M.; Morokuma K.; Zakrzewski V.G.; Voth, G.A.; Salvador P.; Dannenberg J.J.; Dapprich S.; Daniels A.D.; Farkas O.; Foresman J.B.; Ortiz J.V.; Cioslowski J.; Fox D.J.: Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, **2010**.