An Effective Nitrilimine Cycloaddition for Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles from Oximes with Hydrazonoyl Hydrochlorides

Li-Ya Wang,[b] Wen-Che Tseng,[a] Hui-Yi Lin,[c] and Fung Fuh Wong,[a,*]

[a]Graduate Institute of Pharmaceutical Chemistry, China Medical University, No. 91 Hsueh-Shih Rd. Taichung, Taiwan 40402, R.O.C.

[b]The Ph.D. Program for Cancer Biology and Drug Discovery, China Medical University, No. Hsueh- 91, Shih Rd. Taichung, Taiwan 40402, R.O.C.

[c]School of Pharmacy, China Medical University, No. Hsueh- 91, Shih Rd. Taichung, Taiwan 40402, R.O.C.

*Corresponding Author. Tel.: +886 4 220 53366 ext. 5603; Fax: +886 4 220 78083.

E-mail address: ffwong@mail.cmu.edu.tw; wongfungfuh@yahoo.com.tw (F. F. Wong).

Abstract: An effective 1,3-dipolar cycloaddition for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole derivatives was developed by reacting oximes with hydrazonoyl hydrochlorides using triethylamine as a base. The desired 1,3,5-trisubstituted 1,2,4-triazoles were obtained in good yields and the reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates.

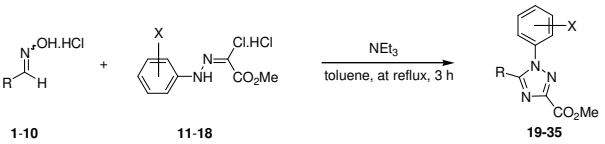
Key words: 1,2,4-Triazoles, hydrazonoyl hydrochloride, nitilimine, 1,3-dipolar cycloaddition, oximes

1,2,4-Triazole is an important class of heterocyclic compounds responsible for the biological activity of many pharmaceutically active compounds that show significant antifungal,[1-3] antiviral,[4] anti-inflammatory,[5] anti-asthmatic,[6] antiproliferative,[7,8] hypotonic activities,[9] antibacterial, and antihelmintic activities.[10] Some molecules based on triazole moiety also act as potent agonist or antagonist receptor ligands,[11,12] and the more selective alkylating agents for the anticancer drugs.[13] Recently, they were developed as mimics[14,15] or isosteres[16] of the amide bond in attempts to increase bioavailability of the parent bioactive molecules.[17] Furthermore, triazole-based agonists or antagonists targeting different receptors were described,[18,19] especially construction molecules based on the 1,3,5-trisubstituted 1,2,4-triazole scaffold.[20-24]

The conventional method for the preparation of triazole rings contains the dehydrative condensation and the cyclization of an acylamidrazone intermediate two steps.[22] In the dehydrative condensation, the neat thermal fusion was performed between hydrazides and nitriles, or the activated nitriles including an imidate (Pinner reaction) or a thioamide (Pellizzari reaction) to form the acylamidrazone intermediates.[25] The subsequent cyclization of the acylamidrazone intermediate was carried out at the high temperature.[25] The typically procedures often involve high reaction temperatures and long reaction times but give the product in low yield. [26]

Different approaches have been reported by using the amidine reactants to replace nitriles. However, only acetamidine and benzamidine substrates are able to achive good yields.[27] In this paper, we expanded the effective nitrilimine cycloaddition[28] for synthesis of 1,3,5-trisubstituted 1,2,4-triazole derivatives by reacting oximes with hydrazonoyl hydrochlorides using triethylamine as a base. The new developed method is applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates to provide 1,3,5-trisubstituted 1,2,4-triazoles in good yields.

Most of the oxime hydrochlorides **1**–**10** were prepared[29] by reacting the corresponding aldehydes with hydroxylamine hydrochloride, expect for the commercially available acetaloxime **1** and benzaloxime **7**. It is well known that in situ generation of nitrilimines from hydrazonoyl chlorides occurs in homogeneous system by base treatment. Since, hydrazonoyl chlorides were often considered as the precursor for nitritimines in 1,3-dipolar cycloaddition.[28,31] Compounds **11**–**18** were synthesized by the treatment of various anilines with $NaNO_2$/HCl,[30] and then the resulting diazonium salts were reacted with methyl 2-chloroacetoacetate to give hydrazonoyl chlorides **11**–**18**.[31]



1-10 11-18 19-35

Scheme 1

Scheme 1 illustrated the typical reaction condition for the new effective synthesis of 1,3,5-trisubstituted 1,2,4-triazoles. It involves a 1,3-diploar cycloaddition of oxime with hydrazonoyl hydrochloride. The hydrazonoyl hydrochloride is behaved like a nitrilimine as a 1,3-dipole species by base treatment and the potonation oxime is used as electron poor dipolarophile to promote the cycloaddition reaction.[28a,b] The reliable procedure is to add 2.0 equiv of NEt_3 to a toluene solution of oximes and hydrazonoyl hydrochloride in a two-necked flask and reflux for ~2.0 h. After the reaction was completed, the reaction was extracted with CH_2Cl_2, workup, and purified with silica gel column chromatography. The desired 1,3,5-trisubstituted 1,2,4-triazole was often isolated in solid form (see Scheme 1, Table 2, Chart 1, and Chart 2).

To search for the suitable basic agent, we chose acetaloxime **1** as the model to seek for the best reaction condition and concentration of base for the new method (see Scheme 1). When hydrazonoyl hydrochloride **11** was treated with various of base,[30,31] including potassium carbonate (K_2CO_3), diethylamine, *N*,*N*-diisopropylethylamin, 4-dimethylaminopyridine (DMAP), and triethylamine, the nitrilimine intermediate was formed *in situ* and reacted with acetaloxime **1** sub-

sequently The desired 1,3,5-trisubstituted 1,2,4-triazoles **11** was obtained through the standard procedure and the results were depicted in Table 1. We found that the use of 2.0 equivalent of triethylamine gave compound **11** in better isolated yield (89%, see the Table 1). When the concentration of triethylamine was increased from 2.0 to 3.0 equivalent (entry 8) or the reaction time was prolonged to about 3 h (entry 9), however, the isolated yields of compound **11** was dramatic reducing from 89% to in 81% and 87%, respectively (see entries 8–9 in Table 1).

Table 1. The Study of Base Promoted 1,3-Diploar Cycloaddition of Acetaloxime **1** with Hydrazonoyl Hydrochloride **11**.

Entry	Base	Equiv[a]	R.T. (h)	1,3,5-trisubstituted 1,2,4-triazole **19** Yields (%)
1	-	-	> 4	Non-detectable
2	K_2CO_3	1.0	2	52
3	Diethylamine	1.0	2	5
4	*N*,*N*-Diisopropylethylamine	1.0	2	48
5	Dimethylaminopyridine (DMAP)	1.0	2	23
6	Triethylamine	1.0	2	75
7	Triethylamine	2.0	2	89
8	Triethylamine	3.0	2	81
9	Triethylamine	2.0	3	87

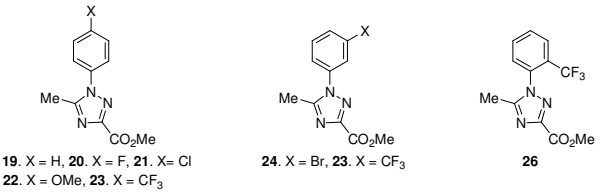
[a]based on the equivalent of acetaloxime **1**.

Furthermore, we investigated the effect of substituent on the phenyl ring of the hydrazonoyl hydrochlorides **12–18** on the reactivity of the reaction. Acetaloxime **1** as the dipolarophile substrates to react with aromatic hydrazonoyl hydrochlorides **12–18** bearing various substituents including F, Cl, Br, CF_3, and OMe at *ortho* or *meta* or *para* position to the nitrilimine group, the reaction gave the corresponding 1,3,5-trisubstituted 1,2,4-triazole products **20–26** in good yields (73–92%, see the entries 1–8 in Table 2). Whatever, the results in Table 2 demonstrated that various substituents on the phenyl ring of the hydrazonoyl hydrochlorides were suitable for the newly developed method. Compounds **19–26** were also fully characterized by spectroscopic methods.[33] Served as an example, compound **19** possessed two characteristic peaks at 153.62 and 154.03 ppm, which represented the ^{13}C in triazole ring. The IR absorptions of **19** showed peaks at 1740 cm^{-1} for the stretching of the –C=O(OMe) carbonyl group. The assignment data of the corresponding product **19** was consistent with the literature data.[31,32]

Table 2. An Effective Synthesis of 1,3,5-trisubstituted 1,2,4-Triazoles by using Oxime Hydrochlorides with Hydrazonoyl Hydrochlorides

Entry	Oxime Hydrochlorides		Hydrazone Hydrochlorides		1,2,4-Triazoles[a]	Yield (%)[b]
	R	No	X	No		
1	Methyl	**1**	H	**11**	**19**	89
2	Methyl	**1**	*p*-F	**12**	**20**	92
3	Methyl	**1**	*p*-Cl	**13**	**21**	86
4	Methyl	**1**	*p*-OMe	**14**	**22**	83
5	Methyl	**1**	*p*-CF_3	**15**	**23**	87
6	Methyl	**1**	*m*-Br	**16**	**24**	92
7	Methyl	**1**	*m*-CF_3	**17**	**25**	83
8	Methyl	**1**	*o*-CF_3	**18**	**26**	80
9	Ethyl	**2**	*p*-F	**12**	**27**	91
10	*i*-Propyl	**3**	*p*-F	**12**	**28**	90
11	Cyclopentyl	**4**	*p*-F	**12**	**29**	88
12	Cyclohexyl	**5**	*p*-F	**12**	**30**	86
13	Phenyl	**6**	*p*-F	**12**	**31**	33
14	2-Naphthyl	**7**	*p*-F	**12**	**32**	28
15	3-Furyl	**8**	*p*-F	**12**	**33**	62
16	3-Thienyl	**9**	*p*-F	**12**	**34**	57
17	2-Pyrrolyl	**10**	*p*-F	**12**	**35**	41

[a]Compound **19** were reported previously,[31] and our spectroscopic data (**19**) isconsistent with published data in the literature. [b]NEt_3 (2 equiv) was used as the base agent.



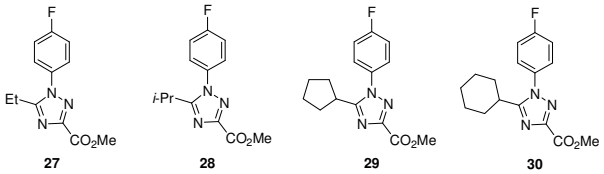


Chart 1

When *p*-fluorophenylchlorohydrazone **12** and triethylamine reacted with aliphatic propionaloxime **2**, *i*-butyloxime **3**, and aliphatic cyclic oxime hydrochlorides including cyclopentanecarboxaldoxime **4** and cyclohexanecarbaldoxime **5**, the 1,3-dipolar cycloaddition also proceeded to provide the corresponding 1,3,5-trisubstituted 1,2,4-triazole products **27–30** in 86–91% yields (see the entries 9–12 of Table 2). Sterically hindered oximes do not appear to hamper the reaction. More specifically, application of the same procedure by using benzaloxime **7** and β-naphthaldoxime **8** gave the poor

results (28–33%, see the entries 13–14 of Table 2). For the further demonstration of the reactivity of aromatic dipolarophiles, various heterocyclic oxime hydrochlorides involving β-furaldoxime **8**, 3-thiophenecarboxaldoxime **9**, and 2-pyrrolecarboxaldoxime **10** were reacted toward *p*-fluorophenylchlorohydrazone **12** under the same basic condition. The moderate yields were also achieved using these substrates (41–62%, see Table 2). Due to the electronic contributions, aromatic and heterocyclic oxime hydrochlorides **6**–**10** own a planar or nearly planar iminium bond configuration to delocalize the electron-density of –C=N$^+$ on oxime moieties and reduce the reactivity of dipolarphile reactants.[34] The experimental result was consistent with the literature data, the cycloaddition outcome was usually satisfactory with alkyl substituted oximes (R = Me, Et, *i*-propyl, cyclopentyl, and cyclohexyl).[28a] As a result, the lower cycloadduct yields were observed in these electron-rich aromatic and heterocyclic oxime dipolarophiles. However, all of the desired 1,3,5-trisubstituted 1,2,4-triazole products **27**–**35** were fully characterized by spectroscopic methods to confirm the structure (see Chart 1 and Chart 2).[35]

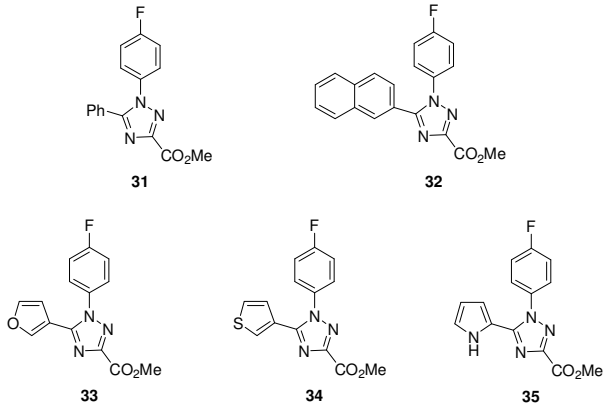
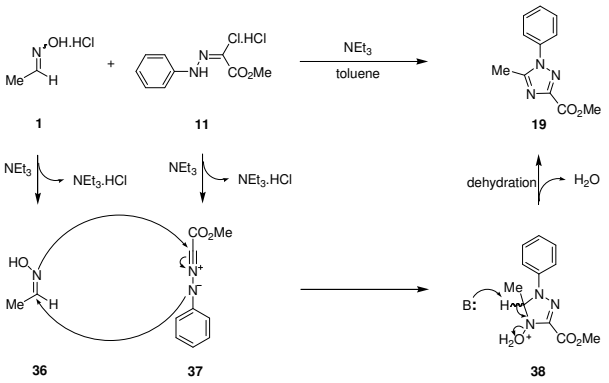


Chart 2

Scheme 2 illustrated the plausible mechanism for the effective 1,3-dipolar cycloaddition for synthesis of 1,3,5-trisubstituted 1,2,4-triazoles. Acetaloxime **1** was reacted with 1.0 equivalent of hydrazonoyl hydrochloride **11** and 2.0 equivalent of triethylamine in toluene at reflux within 1–2 h. In the initially step, hydrazonoyl hydrochloride **11** was successfully converted to a nitrilimine species **37**, behaving like 1,3-dipole in the presence of triethylamine. The requisite 1,3-dipolar cycloadduct dihydrotriazole **38** was *in situ* formed by treating nitrilimine intermediates **37** with dipolarophile oxime **1**. Furthermore, the subsequent dehydration condensation was completed, the corresponding 1,3,5-trisubstituted 1,2,4-triazole product **19** was achieved in high yield (93%, see Scheme 3).



Scheme 2

In conclusion, we have successfully developed an effective 1,3-dipolar cycloaddition for synthesis of 1,3,5-trisubstituted 1,2,4-triazoles by reacting oxime hydrochlorides with hydrazonoyl hydrochlorides. The newly development methodology is applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates and the corresponding 1,2,4-triazole products could be obtained in good yields. More specially, aliphatic or cyclic aliphatic oxime hydrochlorides were appropriate dipolarophile reactants.

References

(1) Collin, X.; Sauleau, A.; Coulon, *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 2601–2605.

(2) Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Le Baut, G.; Marchand, P.; Le Borgne, M. *Tetrahedron Lett.* **2006**, *47*, 6479–6483.

(3) Papakonstantinou-Garoufalias, S.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. *Farmaco* **2002**, *57*, 973–977.

(4) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.

(5) Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **2007**, *15*, 1976–1982.

(6) Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019–3029.

(7) Ouyang, X. H.; Chen, X. L.; Piatnitski, E. L.; Kiselyov, A. S.; He, H. Y.; Mao, Y. Y.; Pattaropong, V.; Yu, Y.; Kim, K. H.; Kincaid, J.; Smith, L.; Wong, W. C.; Lee, S. P.; Milligan, D. L.; Malikzay, A.; Fleming, J.; Gerlak, J.; Deevi, D.; Doody, J. F.; Chiang, H. H.; Patel, S. N.; Wang, Y.; Rolser, R. L.; Kussie, P.; Labelle, M.; Tuma, M. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5154–5159.

(8) Saha, A. K.; Liu, L.; Simoneaux, R.; DeCorte, B.; Meyer, C.; Skrzat, S.; Breslin, H. J.; Kukla, M. J.; End, D. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5407–5411.

(9) Hester, J. B., Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078–1081.

(10) (a) Hardman, J.; Limbird, L.; Gilman, A. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed.; McGraw-Hill: New York, 1996; p. 988; (b) Gennaro, A. R.; Remington. In *The Science and Practice of Pharmacy*, Mack Easton, PA, 1995; Vol. II, pp 1327; (c) Richardson, K.; Whittle, P. J. *Eur. Pat. Appl. EP* **1984**, *115*, 416; Richardson, K.; Whittle, P. J. *Chem. Abstr.* **1984**, *101*, 230544; (d) Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S.; Meyer, N. *Brighton Crop Prot. Conf. Pests. Dis.* **1990**, *2*, 407; Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S.; Meyer, N. *Chem. Abstr.* **1991**, *114*, 223404h; (e) Heindel, N. D.; Reid, J. R. *J. Heterocycl. Chem.* **1980**, *17*, 1087–1088.

(11) Chen, C.; Dagnino, R.; Huang, C. Q.; McCarthy, J. R.; Grigoriadis, D. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3165–3168.

(12) Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392–2406.

(13) De las Heras, F. G.; Alonso, R.; Alonso, G. *J. Med. Chem.* **1979**, *22*, 496–501.

(14) Burrell, G.; Evans, J. M.; Hadley, M. S.; Hicks, F.; Stemp, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1285–1290.

(15) (a) Thompson, S. K.; Eppley, A. M.; Frazee, J. S.; Darcy, M. G.; Lum, R. T.; Tomaszek, T. A.; Ivanoff, L. A.; Morris, J. F.; Sternberg, E. J.; Lambert, D. M.; Fernandez, A. V.; Petteway, S. R.; Meek, T. D.; Metcalf, B. W.; Gleason, J. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2441–2446; (b) Tully, W. R.; Gardner, C. R.; Gillepsie, R. J.; Westwood, R. J. *J. Med. Chem.* **1991**, *34*, 2060–2067.

(16) (a) Hitotsuyanagi, Y.; Motegi, S.; Fukaya, H.; Takeya, K. *J. Org. Chem.* **2002**, *67*, 3266–3271; (b) Boyd, S. A.; Fung, A. K. L.; Baker, W. R.; Mantei, R. A.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Klinghofer, V.; Wessale, J. L.; Verburg, K. M.; Polakowski, J. S.; Adler, A. L.; Calzadilla, S. V.; Kovar, P.; Yao, Z.; Hutchins, C. W.; Denissen, J. F.; Grabowski, B. A.; Cepa, S.; Hoffman, D. J.; Garren, K. W.; Kleinert, H. D. *J. Med. Chem.* **1994**, *37*, 2991–3007.

(17) Duncia, J. V.; Santela, J. B., III; Higley, A.; VanAtten, M. K.; Weber, P. C.; Alexander, R. S.; Kettner, C. A.; Pruitt, J. R.; Liauw, A. Y.; Quan, M. L.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 775–780.

(18) Contour-Galcera, M. O.; Sidhu, A.; Plas, P.; Roubert, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3555–3559.

(19) Jagerovic, N.; Hemandez-Folgado, L.; Alkorta, I.; Goya, P.; Martin, M. I.; Dannert, M. T.; Alsasua, A.; Frigola, J.; Cuberes, M. R.; Dordal, A.; Holenz, J. *Eur. J. Med. Chem.* **2006**, *41*, 114–120.

(20) Alanine, A.; Anselm, L.; Steward, L.; Thomi, S.; Vifian, W.; Groaning, M. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 817–821.

(21) Dumaĭtre, B.; Dodic, N. *J. Med. Chem.* **1996**, *39*, 1635–1644.

(22) Yeung, K.-S.; Farkas, M. E.; Kadow, J. F.; Meanwell, N. A. *Tetrahedron Lett.* **2005**, *46*, 3429–3432.

(23) Liu, C. ; Iwanowicz, J. *Tetrahedron Lett.* **2003**, *44*, 1409–1411.

(24) Abdel-Megeed, A. M.; Abdel-Rahman, H. M.; Alkaramany, G.-E. S.; El-Gendy, M. A. *Eur. J. Med. Chem.* **2009**, *44*, 117–123.

(25) (a) Castanedo, G. M.; Seng, P. S.; Blaquiere, N.; Trapp, S.; Staben, S. T. *J. Org. Chem.* **2011**, *76*, 1177–1179; (b) Weidinger, H.; Kranz, J. DE Patent 1076136, **1958**; (c) Neelima, A.; Bhaduri, A. P. *Indian J. Chem.* **1993**, *22B*, 79.

(26) (a) Olesen, P. H.; Sorensen, A. R.; Urso, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *38*, 3333–3341; (b) Breslin, H. J.; Miskowski, T. A.; Kukla, M. J.; De Winter, H. J.; Somers, M. V. F.; Roevens, P. W. M.; Kavash, R. W. D. *Bioorg. Med. Chem. Lett.* 2003, *13*, 4467–4471; (c) Baldwin, J. J.; Kasinger, P. A.; Novello, F. C.; Spradue, J. M.; Duggen, D. E. *J. Med. Chem.* **1975**, *18*, 895–900.

(27) Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. *Tetrahedron Lett.* **1987**, *28*, 5133–5136.

(28) (a) Molteni, G.; Del Buttero, P. *Heterocycles* **2005**, *65*, 1183–1188; (b) Giorgio Molteni, G.; Alessandro Pontib, A.; Orlandi, M *New J. Chem.* **2002**, *26*, 1346–1351; (c) Ponti, A.; Giorgio Molteni, G. *New J. Chem.* **2002**, *26*, 1340–1345; (d) Caramella P.; Grünanger, P. in *1,3-Dipolar Cycloaddition Chemistry*, ed. Padwa, A. Wiley-Interscience, New York, USA, 1984, vol. 1, ch. 3; (e) Broggini, G.; Molteni G.; Zecchi, G. *Heterocycles* **1998**, *47*, 541–549; (f) Luheshi, A.-B. N.; Smalley, R. K. *Tetrahedron Lett.* **1990**, *31*, 127–130.

(29) (a) Grigorjeva1, A.; Jirgensons1, A.; Domracheva1, I.; Yashchenko1,E.; Shestakova1, I.; Andrianov1, V.; Kalvinsh, I. *Chem. Heterocycl. Comp.* **2009**, *45*, 161–168; (b) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Steven P. Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197–1202.

(30) Broggini, G.; Casalone, G.; Garanti, L.; Molteni, G.; Pilati, T.; Zecchi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 4447–4554.

(31) (a) Pfefferkorn, J. A.; Choi, C.; Larsen, S. D.; Auerbach, B.; Hutchings, R.; Park, W.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G. H.; Robertson, A.; Sekerke, C.; Harris,cM. S.; Pavlovsky, A.; Bainbridge, G.; Caspers, N.; Kowala,

M.; Tait, B. D. *J. Med. Chem.* **2008,** *51,* 31–45; (b) Silvestri, R.; Cascio, M. G.; Regina, G. L.; Piscitelli, F.; Lavecchia, A.; Brizzi, A.; Pasquini, S.; Botta, M.; Novellino, E.; Marzo, V. D.; Corelli, F. *J. Med. Chem.* **2008,** *51,* 1560–1576; (c) Pinto, D. J. P.; Orwat, M. J.; Koch, S.; Rossi, K. A.; Alexander, R. S.; Smallwood, A.; Wong, P. C.; Rendina, A. R.; Luettgen, J. M.; Knabb, R. M.; He, K.; Xin, B.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2007,** *50,* 5339–5356; (d) Luca, B.; Luisa, G.; Gaetano, Z. *Synthesis* **1986,** 772–774; (e) Luca, B.; Luisa, G.; Gaetano, Z. *Synthesis* **1985,** 304–305.

(32) Bruché, L.; Garanti, L.; Zecchi, G. *J. Chem. Research (S)* **1989**, 16–17.

(33) **Standard Procedure of 1,3-diplar Cycloaddition for Synthesis of 1,3,5-trisubstituted 1,2,4-Triazoles (19-35).** A solution of oxime derivatives (**1–10**, 1.0 mmol, 1.0 equiv) and triethylamine (2.0 mmol, 2.0 equiv) with various of hydrazonoyl hydrochlorides (**11–18**, 1.0 mmol, 1.0 equiv) in toluene solution (6 mL) at reflux within 1–2 h. When the reaction was completed, the reaction mixture was concentrated, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 1,3,5-trisubstituted 1,2,4-Triazole products (**19**–**35**) in 28–92% yields.

20: yellow solid; mp 169–170 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3 H , CH_3), 3.92 (s, 3 H , CH_3), 7.10–7.18 (m, 2 H, ArH), 7.36–7.43 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.02, 52.73, 116.35 (*C–CF), 116.82 (*C–CF), 126.81 (*C=C–CF), 126.99 (*C=C–CF), 132.75, 153.71, 154.15 (*CF), 160.29, 165.28; IR (diffuse reflectance) 2963 (m), 1739 (s, C=O), 1516 (m), 1474 (m), 1427 (m), 1219 (m), 1150 (m), 845 (m), 810 (m), 671 (m) cm^{-1}; MS (ESI) *m/z*: 235 (M^+ + 1); Anal. Calcd for $C_{11}H_{10}F N_3O_2$; C: 56.17; H: 4.29; N: 17.86, Found: C: 56.14; H: 4.27; N: 17.87.

(34) (a) Möller, C.; Plsset, M. S. *Phys. Rev.* **1934**, *46*, 618–622; (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P.v. R. *J. Comput. Chem.* **1983**, *3*, 294–301.

(35) **27:** light yellow solid; mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3 H, *J* = 7.54 Hz, CH_3), 2.77 (q, 2 H, *J* = 7.54 Hz, CH_2), 3.93 (s, 3 H , CH_3), 7.12–7.21 (m, 2 H, ArH), 7.37–7.44 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.85, 19.97, 52.63, 116.27 (*C–CF), 116.73 (*C–CF), 127.11 (*C=C–CF), 127.29 (*C=C–CF), 132.59, 153.67, 159.02 (*CF), 160.20, 165.25; IR (diffuse reflectance) 2986 (m), 1740 (s, C=O), 1520 (m), 1373 (m), 1204 (m), 1018 (m), 964 (m), 853 (m), 607 (m) cm^{-1}; MS (ESI) *m/z*: 249 (M^+ + 1); Anal. Calcd for $C_{12}H_{12}FN_3O_2$; C: 57.90; H: 4.87; N: 16.86, Found: C: 57.87; H: 4.89; N: 16.88.