One-Pot Multicomponent Synthesis of 1-Aryl-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides: An Easy Procedure for Combinatorial Chemistry

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Received January 26, 2009

A convenient synthetic protocol was elaborated for creation of combinatorial libraries of 1-(R^1-phenyl)-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides. As starting materials, commercially available or readily prepared azides, amines, and diketene were selected for the reaction which has proceeded in a one-pot system with high yields and in short time.

Introduction

New developments in the search for novel pharmacological agents over the past decade have focused on the preparation of chemical libraries as sources for new leads for drug discovery.[1] Multicomponent reactions (MCRs) are of increasing importance for such findings.[1−7] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process,[6] multicomponent strategies offer significant advantages over conventional linear-type syntheses.[1−7] In such reactions, three or more reactants come together in a single reaction vessel to form novel products that contain fragments of all the components. The search and discovery of new MCRs are of considerable current interest.

In the current work, we have elaborated a new type of multicomponent reaction which gives wide access to triazole derivatives production. It is well-known that triazoles are very attractive targets for combinatorial library synthesis because of their broad range of pharmaceutical activities. They have been reported to be inhibitors of glycogen synthase kinase-3,[8] antagonists of GABA receptors,[9,10] agonists of muscarine receptors,[11] neuroleptic,[12] and also compounds, showing anti-HIV-1,[13] cytotoxic,[14] antihistaminic,[15] and antiproliferative activities.[16] Moreover, the triazole fragment includes an antibiotic *Cefatricin*[17,18] and anticonvulsant drug *Rufinamide*.[19]

The synthesis of multisubstituted triazoles has attracted much attention, and a number of procedures have been developed.[20] However, they all rely on multistep reactions. The 1,3-dipolar cycloaddition reaction of azides with acetylenes is commonly used in triazole syntheses. The main problem of such reactions deals with poor regioselectivity and hard experimental conditions. However, there is no data concerning the reaction of azides with various methylenic components under the MCR strategy in the literature. Therefore, we report our efforts toward the development of a facile, atom-economical, solution-phase parallel synthetic protocol of triazole synthesis using an MCR-like tandem methodology.

Results and Discussion

We have selected commercially available or easily prepared azides, amines, and diketene as individual building blocks since they cover a wide range of structural variations. Therefore, combining these fragments in one reaction may be very attractive from a biological point of view.[20−22] It is known that azides easily and regioselectively react with acetoacetic acids esters as well as amides.[23] These reactions undergo a base catalysis and complete within 1 h. In addition, one of the most convenient methods to prepare acetoacetic acid amides is the reaction of amines with diketene.[24] The formation of acetoacetamides can be accelerated by adding tertiary amines.[25] These reactions are rapid and proceed with high yields. However, there is no information about the reaction of azides with diketene. So we can make up the presumption that above cited reactions can be performed in a parallel and/or consecutive fashion in a one-pot system.

We have selected a number of experimental conditions to carry out such reactions, e.g. the following base/solvent systems: Et_3N/acetonitrile, Et_3N/dioxane, *t*-BuOK/DMSO, Et_3N/benzen, pyridine. It was found that acetonitrile medium and Et_3N, as a base catalyst, showed an excellent result. The other base/solvent systems were subsequently less effective.

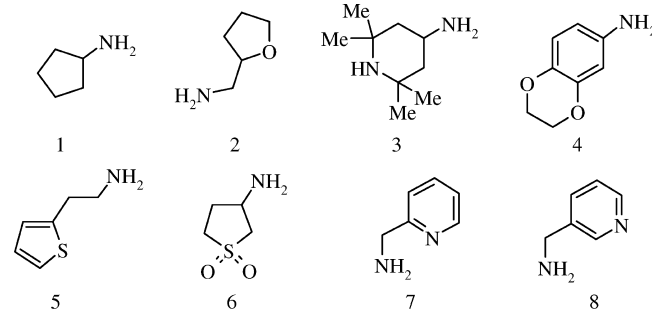

Figure 1. Diversity of the reagents **3**{1−8}.

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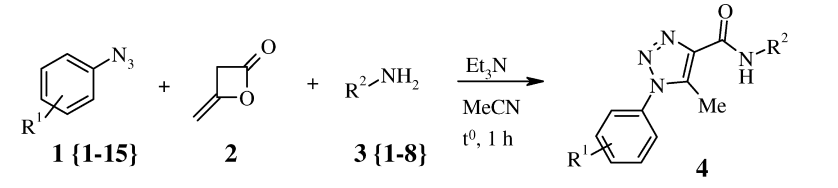
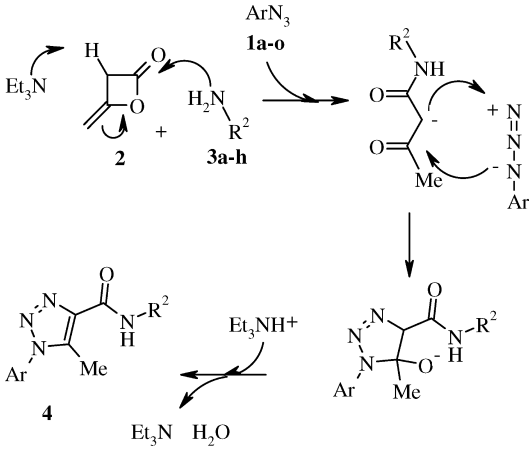
10.1021/cc900012w CCC: $40.75
Published on Web 04/21/2009

Scheme 1. Synthesis of Amides **4**



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
R^1	H	2-Me	3-Me	4-Me	4-Bu	4-*i*Pr	2-F	4-F	2-Cl	3-Cl	4-I	2-MeO	3-MeO	4-MeO	4-PrO

Scheme 2. Plausible Reaction Mechanism



In the *t*-BuOK/DMSO system and pyridine solution, the yields of triazoles were poor; on the other hand, in Et_3N/dioxane and Et_3N/benzene systems, the triazole yields were moderated, but extraction of the products was more laborious. Arylazides reacted with diketene and appropriate amines (see Figure 1) in the Et_3N/acetonitrile system formed 1-(R^1-phenyl)-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides in high yields (Scheme 1).

Reaction time correlates with reactivity of azides and on average lasts approximately 30 min. Furthermore, the reaction of diketene with highly nucleophilic amines and reactive azides proceeds at room temperature longer than when heating under reflux. The yields of the reactions increase with an increase of amine basicity. Reactions were monitored by thin-layer chromatography (TLC) and the disappearance of the characteristic azide absorption band in the IR spectrum.

In addition, the advantage of such methodology (protocol) is that in several cases products sedimented from the reaction medium after cooling it to room temperature. Amides were of a high purity, and none of the byproduct was registered.

The structures of compounds **4** were deduced from their elemental analysis, ^1H ^{13}C NMR spectra, and mass spectra. No other products except **4** were detected.

A possible explanation of the mechanism for the reaction was depicted in Scheme 2. Initially, the attack of diketene **2** carbonyl group by amino moiety **3** led to the formation of acetoacetic amides. At the same time a base generated carboanion in the position 2 of amide. Then, Dimroth cyclocondensation started by nucleophilic attack of terminal nitrogen in azido group. The following ring formation with elimination of water yielded triazole **4**. The reaction presum-

Table 1. Analytical Data of 1-(R^1-Phenyl)-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides **4**

			elemental analyses *calcd* found							
entry	product	molecular formula	% C	% H	% N	MS (EI) *m/z*	IR, ν (cm^{-1})	Mp (°C)	yield (%)	purity[a] (%)
1	**4**{1,1}	$C_{15}H_{18}N_4O$	*66.64* 66.37	*6.71* 6.59	*20.73* 20.93	270	1662 (CO); 3350 (NH)	134	85	100
2	**4**{5,1}	$C_{19}H_{26}N_4O$	*69.91* 69.78	*8.03* 7.84	*17.16* 17.03	326	1655 (CO); 3348 (NH)	125	71	99
3	**4**{10,1}	$C_{15}H_{17}ClN_4O$	*59.11* 59.03	*5.62* 5.87	*18.38* 18.24	304	1680 (CO); 3365 (NH)	107	75	100
4	**4**{1,2}	$C_{15}H_{18}N_4O_2$	*62.92* 62.64	*6.34* 6.17	*19.57* 19.43	286	1660 (CO); 3330 (NH)	83	69	97
5	**4**{9,2}	$C_{15}H_{17}ClN_4O_2$	*56.16* 55.82	*5.34* 5.28	*17.47* 17.30	320	1655 (CO); 3338 (NH)	68	86	100
6	**4**{11,2}	$C_{15}H_{17}IN_4O_2$	*43.70* 43.74	*4.16* 4.07	*13.59* 13.44	412	1685 (CO); 3370 (NH)	79	94	100
7	**4**{15,2}	$C_{18}H_{24}N_4O_3$	*62.77* 62.51	*7.02* 7.18	*16.27* 16.46	344	1657 (CO); 3310 (NH)	89	80	99
8	**4**{1,3}	$C_{19}H_{27}N_5O$	*66.83* 66.69	*7.97* 7.77	*20.51* 20.72	341	1692 (CO); 3140, 3390 (NH)	132	84	100
9	**4**{12,3}	$C_{20}H_{29}N_5O_2$	*64.66* 64.79	*7.87* 7.63	*18.85* 18.68	371	1675 (CO); 3138, 3371 (NH)	122	58	100
10	**4**{13,3}	$C_{20}H_{29}N_5O_2$	*64.66* 64.48	*7.87* 7.99	*18.85* 18/81	371	1688 (CO); 3130, 3385 (NH)	109	74	99
11	**4**{1,4}	$C_{18}H_{16}N_4O_3$	*64.28* 64.11	*4.79* 4.56	*16.66* 16.90	336	1680 (CO); 3370 (NH)	171	89	100
12	**4**{1,5}	$C_{16}H_{16}N_4OS$	*61.52* 61.39	*5.16* 5.02	*17.93* 17.99	312	1645 (CO); 3302 (NH)	111	91	99
13	**4**{4,5}	$C_{17}H_{18}N_4OS$	*62.55* 62.57	*5.56* 5.42	*17.16* 16.97	326	1633 (CO); 3312 (NH)	102	91	100
14	**4**{13,5}	$C_{17}H_{18}N_4O_2S$	*59.63* 59.78	*5.30* 5.12	*16.36* 16.17	342	1640 (CO); 3300 (NH)	101	74	98
15	**4**{14,5}	$C_{17}H_{18}N_4O_2S$	*59.63* 59.48	*5.30* 5.03	*16.36* 16.57	342	1638 (CO); 3298 (NH)	123	85	100
16	**4**{1,6}	$C_{14}H_{16}N_4O_3S$	*52.49* 52.33	*5.03* 5.17	*17.49* 17.41	320	1670 (CO); 3385 (NH)	218	72	98
17	**4**{4,6}	$C_{15}H_{18}N_4O_3S$	*53.88* 53.69	*5.43* 5.30	*16.75* 16.92	334	1665 (CO); 3372 (NH)	200	60	99
18	**4**{7,6}	$C_{14}H_{15}FN_4O_3S$	*49.70* 49.57	*4.47* 4.51	*16.56* 16.43	338	1685 (CO); 3395 (NH)	234	53	100
19	**4**{8,6}	$C_{14}H_{15}FN_4O_3S$	*49.70* 49.84	*4.47* 4.32	*16.56* 16.68	338	1690 (CO); 3399 (NH)	183	69	98
20	**4**{1,7}	$C_{16}H_{15}N_5O$	*65.52* 65.67	*5.15* 4.97	*23.88* 23.54	293	1655 (CO); 3348 (NH)	112	77	99
21	**4**{2,7}	$C_{17}H_{17}N_5O$	*66.43* 66.55	*5.58* 5.75	*22.79* 22.97	307	1652 (CO); 3340 (NH)	101	56	100
22	**4**{3,7}	$C_{17}H_{17}N_5O$	*66.43* 66.37	*5.58* 5.30	*22.79* 22.50	307	1662 (CO); 3350 (NH)	117	69	99
23	**4**{6,7}	$C_{19}H_{21}N_5O$	*68.04* 68.22	*6.31* 6.22	*20.88* 20.69	335	1665 (CO); 3348 (NH)	119	74	100
24	**4**{12,7}	$C_{17}H_{17}N_5O_2$	*63.15* 63.00	*5.30* 5.11	*21.66* 21.39	323	1654 (CO); 3288 (NH)	116	68	98
25	**4**{1,8}	$C_{16}H_{15}N_5O$	*65.52* 65.37	*5.15* 5.01	*23.88* 23.81	293	1648 (CO); 3298 (NH)	133	88	100
26	**4**{2,8}	$C_{17}H_{17}N_5O$	*66.43* 66.31	*5.58* 5.36	*22.79* 22.90	307	1655 (CO); 3305 (NH)	101	65	98
27	**4**{8,8}	$C_{16}H_{14}FN_5O$	*61.73* 61.64	*4.53* 4.27	*22.50* 22.29	311	1630(CO); 3320 (NH)	127	79	100
28	**4**{10,8}	$C_{16}H_{14}ClN_5O$	*58.63* 58.81	*4.31* 4.18	*21.37* 21.47	327	1628 (CO); 3283 (NH)	76	91	100

[a] Purity was confirmed by LC.

Table 2. ^{1}H NMR Spectra of Amides **4**

product	^{1}H NMR
4{1,1}	1.57−1.67 (4H, m, H_{cPn}), 1.74−1.81 (2H, m, H_{cPn}), 1.90−1.98 (2H, m, H_{cPn}), 2.57 (3H, s, Me), 4.25−4.32 (1H, m, H_{cPn}), 7.56 (2H, d, ^3J 7.8, H_{Ph}-3,5), 7.60 (1H, m, H_{Ph}-4), 7.62 (2H, d, ^3J 7.8, H_{Ph}-2,6), 8.03 (1H, d, ^3J 7.8, NH)
4{5,1}	0.96 (3H, t, ^3J 7.8, H_{Bu}), 1.39 (2H, m, H_{Bu}), 1.57−1.63 (4H, m, H_{cPn}), 1.65 (2H, m, H_{Bu}), 1.73−1.79 (2H, m, H_{cPn}), 1.88−1.96 (2H, m, H_{cPn}), 2.54 (3H, s, Me), 2.71 (2H, t, ^3J 7.8, H_{Bu}), 4.23−4.30 (1H, m, H_{cPn}), 7.40 (2H, d, ^3J 7.8, H_{Ar}-3,5), 7.43 (2H, d, ^3J 7.8, H_{Ar}-2,6), 8.02 (1H, d, ^3J 8.8, NH)
4{10,1}	1.55−1.65 (4H, m, H_{cPn}), 1.77−1.78 (2H, m, H_{cPn}), 1.88−1.95 (2H, m, H_{cPn}), 2.57 (3H, s, Me), 4.22−4.29 (1H, m, H_{cPn}), 7.54 (1H, dd,^3J 7.8, ^4J 2.0, H_{Ar}-6), 7.60−7.64 (2H, m, H_{Ar}-4,5), 7.67 (1H, s, H_{Ar}-2), 8.06 (1H, d, ^3J 7.8, NH)
4{1,2}	1.61−1.69 (1H, m, H_{Fur}), 1.83−1.97 (3H, m, H_{Fur}), 2.56 (3H, s, Me), 3.29−3.41 (2H, m, CH_2), 3.63−3.70 (1H, m, H_{Fur}), 3.80−3.86 (1H, m, H_{Fur}), 3.97−4.04 (1H, m, H_{Fur}), 7.54 (2H, dd,^3J 7.8, ^4J 2.0, H_{Ph}-2,6), 7.57−7.64 (3H, m, H_{Ph}-3,4,5), 8.12 (1H, t, ^3J 5.9, NH)
4{9,2}	1.64−1.71 (1H, m, H_{Fur}), 1.84−1.99 (3H, m, H_{Fur}), 2.39 (3H, s, Me), 3.33−3.39 (2H, m, CH_2), 3.65−3.71 (1H, m, H_{Fur}), 3.81−3.87 (1H, m, H_{Fur}), 3.98−4.05 (1H, m, H_{Fur}), 7.59−7.62 (2H, m, H_{Ar}-3,4), 7.65−7.71 (1H, m, H_{Ar}-5), 7.73 (1H, d, ^3J 7.8, H_{Ar}-6), 8.19 (1H, t, ^3J 5.9, NH)
4{11,2}	1.61−1.69 (1H, m, H_{Fur}), 1.81−2.00 (3H, m, H_{Fur}), 2.56 (3H, s, Me), 3.30−3.41 (2H, m, CH_2), 3.63−3.71 (1H, m, H_{Fur}), 3.79−3.87 (1H, m, H_{Fur}), 3.96−4.05 (1H, m, H_{Fur}), 7.38 (2H, d, ^3J 7.8, H_{Ar}-3,5), 7.42 (2H, d, ^3J 8.8, H_{Ar}-2,6), 8.08 (1H, t, ^3J 5.9, NH)
4{15,2}	1.06 (3H, t, ^3J 7.8, CH_3), 1.61−1.69 (1H, m, H_{Fur}), 1.81 (2H, m, CH_2), 1.85−1.98 (3H, m, H_{Fur}), 2.51 (3H, s, Me), 3.31−3.40 (2H, m, CH_2), 3.64−3.71 (1H, m, H_{Fur}), 3.80−3.87 (1H, m, H_{Fur}), 3.99 (1H, m, H_{Fur}), 4.01 (2H, t, ^3J 6.8, CH_2O), 7.08 (2H, d, ^3J 8.8, H_{Ar}-3,5), 7.94 (2H, d, ^3J 8.8, H_{Ar}-2,6), 8.07 (1H, t, ^3J 5.9, NH)
4{1,3}	1.10 (6H, s, Me), 1.22 (2H, d, ^2J 12.7, CH_2), 1.24 (6H, s, Me), 1.73 (2H, dd,^3J 3.9, ^2J 12.7, CH_2), 2.57 (3H, s, Me), 4.26−4.36 (1H, m, CH), 7.57 (1H, dt, ^3J 6.8, ^4J 2.0, H_{Ph}-4), 7.60 (2H, m, H_{Ph}-3,5), 7.64 (2H, dd, ^3J 6.8, ^4J 2.0, H_{Ph}-2,6), 7.89 d (1H, ^3J 8.8, NH)
4{12,3}	1.07 (6H, s, Me), 1.18 (2H, d, ^2J 12.7, CH_2), 1.21 (6H, s, Me), 1.72 (2H, dd, ^3J 3.9, ^2J 12.7, CH_2), 2.34 (3H, s, Me), 3.82 (3H, s, MeO), 4.24−4.34 (1H, m, CH),7.13 (1H, t, ^3J 7.8, H_{Ar}-4), 7.26 (1H, d, ^3J 7.8, H_{Ar}-3), 7.35 (1H, d, ^3J 7.8, H_{Ar}-6), 7.58 (1H, t, ^3J 7.8, H_{Ar}-5), 7.80 (1H, d, ^3J 7.8, NH)
4{13,3}	1.07 (6H, s, Me), 1.19 (2H, d, ^2J 12.7, CH_2), 1.22 (6H, s, Me), 1.71 (2H, dd, ^3J 3.9, ^2J 12.7, CH_2), 2.55 (3H, s, Me), 3.85 (3H, s, MeO), 4.25−4.34 (1H, m, CH), 7.07 (1H, d, ^3J 7.8, H_{Ar}-4), 7.08 (1H, d, ^3J 7.8, H_{Ar}-6), 7.12 (1H, s,H_{Ar}-2), 7.49 (1H, t, ^3J 7.8, H_{Ar}-5), 7.84 (1H, d, ^3J 7.8, NH)
4{1,4}	2.61 (3H, s, Me), 4.22 (4H, dd, ^3J 4.9, ^3J 8.8, CH_2), 6.73 (1H, d, ^3J 8.8, H_{Ar}-5), 7.26 (1H, dd, ^3J 8.8, ^4J 2.9, H_{Ar}-6), 7.44 (1H, d, ^3J 2.0, H_{Ar}-2), 7.57−7.66 (5H, m, H_{Ph}), 10.1 s (1H, NH)
4{1,5}	2.58 (3H, s, Me), 3.11 (2H, t, ^3J 7.8, CH_2), 3.57 (2H, dt, ^3J 7.8, ^3J 5.9, CH_2), 6.90 (1H, d, ^3J 2.9, H_{Th}-3), 6.94 (1H, m, H_{Th}-4), 7.20 (1H, d, ^3J 4.9, H_{Th}-5), 7.55 (2H, dd, ^3J 7.8, ^4J 2.0, H_{Ph}-2,6), 7.59−7.66 (3H, m, H_{Ph}-3,4,5), 8.55 t (1H, ^3J 5.9, NH)
4{4,5}	2.45 (3H, s, Me), 2.54 (3H, s, Me), 3.08 (2H, t, ^3J 6.8, CH_2), 3.55 (2H, q, ^3J 6.8, CH_2), 6.88 (1H, d, ^3J 2.9, H_{Th}-3), 6.92 (1H, dd, ^3J 2.9, ^3J 4.9, H_{Th}-4), 7.20 (1H, d, ^3J 4.9, H_{Th}-5), 7.39 (2H, d, ^3J 8.8, H_{Ar}-3,5), 7.41 (2H, d, ^3J 8.8, H_{Ar}-2,6), 8.50 (1H, t, ^3J 5.9, NH)
4{13,5}	2.59 (3H, s, Me), 3.11 (2H, t, ^3J 6.8, CH_2), 3.57 (2H, q, ^3J 6.8, CH_2), 3.87 (3H, s, Me), 6.90 (1H, d,^3J 2.9, H_{Th}-3), 6.94 (1H, m, H_{Th}-4), 7.12 (3H, m, H_{Ar}-2,3,4), 7.20 (1H, d, ^3J 3.9, H_{Th}-5), 7.51 (1H, dd, ^3J 7.8, ^4J 2.0, H_{Ar}-2), 8.53 (1H, t, ^3J 5.9, NH)
4{14,5}	2.51 (3H, s, Me), 3.08 (2H, t, ^3J 6.8, CH_2), 3.55 (2H, q, ^3J 6.8, CH_2), 3.86 (3H, s, MeO), 6.88 (1H, d, ^3J 2.9, H_{Th}-3), 6.91 (1H, m, H_{Th}-4), 7.10 (2H, d, ^3J 8.8, H_{Ar}-3,5), 7.19 (1H, d, ^3J 4.9, H_{Th}-5), 7.44 (2H, d, ^3J 8.8, H_{Ar}-2,6), 8.48 (1H, t, ^3J 5.9, NH)
4{1,6}	2.30−2.39 (1H, m, H_{Th}), 2.40−2.48 (1H, m, H_{Th}), 2.57 (3H, s, Me), 3.13−3.26 (2H, m, H_{Th}), 3.30−3.41 (2H, m, H_{Th}), 4.71−4.79 (1H, m, H_{Th}), 7.54−7.60 (3H, m, H_{Ph}-3,4,5), 7.62 (2H, d, ^3J 7.8, H_{Ph}-2,6), 8.98 (1H, d, ^3J 7.8, NH)
4{4,6}	2.30−2.38 (1H, m, H_{Th}), 2.40−2.45 (1H, m, H_{Th}), 2.46 (3H, s, Me), 2.54 (3H, s, Me), 3.13−3.25 (2H, m, H_{Th}), 3.31−3.40 (2H, m, H_{Th}), 4.71−4.79 (1H, m, H_{Th}), 7.40 (2H, d, ^3J 8.8, H_{Ar}-3,5), 7.42 (2H, d, ^3J 8.8, H_{Ar}-2,6), 8.96 (1H, d, ^3J 7.8, NH)
4{7,6}	2.30−2.39 (1H, m, H_{Th}), 2.40−2.48 (1H, m, H_{Th}), 2.46 (3H, s, Me), 3.15−3.25 (2H, m, H_{Th}), 3.31−3.40 (2H, m, H_{Th}), 4.70−4.80 (1H, m, H_{Th}), 7.47 (1H, m, H_{Ar}-5), 7.52 (1H, d, ^3J 8.8, H_{Ar}-6), 7.62 (1H, dt, ^3J 7.8, ^4J 2.0, H_{Ar}-4), 7.70 (1H, ddd, ^3J 7.8, ^3J 6.8, ^4J 2.0, H_{Ar}-3), 9.02 (1H, d, ^3J 7.8, NH)
4{8,6}	2.31−2.39 (1H, m, H_{Th}), 2.41−2.48 (1H, m, H_{Th}), 2.55 (3H, s, Me), 3.12−3.25 (2H, m, H_{Th}), 3.31−3.40 (2H, m, H_{Th}), 4.71−4.80 (1H, m, H_{Th}), 7.40 (2H, t, ^3J 8.8, H_{Ar}-3,5), 7.63 (2H, dd, ^3J 8.8, ^3J 4.9, H_{Ar}-2,6), 8.99 (1H, d, ^3J 7.8, NH)
4{1,7}	2.59 (3H, s, Me), 4.63 (2H, d, ^3J 5.8, CH_2), 7.22 (1H, dd, ^3J 6.8, ^3J 4.9, H_{Py}-5), 7.36 (1H, d, ^3J 7.8, H_{Py}-3), 7.57−7.67 (5H, m, H_{Ph}), 7.72 dt (1H, ^3J 7.8,^4J 2.0, H_{Py}-4), 8.52 (1H, d, ^3J 4.9, H_{Py}-6), 8.96 (1H, t, ^3J 5.8, NH)
4{2,7}	2.04 (3H, s, Me), 2.37 (3H, s, Me), 4.61 (2H, d, ^3J 5.8, CH_2), 7.21 (1H, dd, ^3J 6.8, ^3J 4.9, H_{Py}-5), 7.33 (1H, d, ^3J 7.8, H_{Py}-3), 7.37 (1H, d, ^3J 7.8, H_{Ar}-3), 7.42 (1H, dd, ^3J 7.8, ^3J 6.8, H_{Ar}-4), 7.48 (1H, t, ^3J 6.8, H_{Ar}-5), 7.54 (1H, d, ^3J 6.8, H_{Ar}-6), 7.71 (1H, t, ^3J 7.8, H_{Py}-4), 8.50 (1H, d, ^3J 4.9, H_{Py}-6), 8.94 (1H, t, ^3J 5.8, NH)
4{3,7}	2.46 (3H, s, Me), 2.57 (3H, s, Me), 4.60 (2H, d, ^3J 5.8, CH_2), 7.21 (1H, m, H_{Py}-5), 7.34 (1H, d, ^3J 7.8, H_{Ar}-4), 7.35 (1H, d, ^3J 7.8, H_{Ar}-2), 7.37 (1H, s, H_{Ar}-2), 7.38 (1H, d, ^3J 7.8, H_{Py}-3), 7.48 (1H, t, ^3J 7.8, H_{Ar}-5), 7.70 (1H, dt, ^3J 7.8,^4J 2.0, H_{Py}-4), 8.50 d (1H, ^3J 4.9, H_{Py}-6), 8.92 (1H, t, ^3J 5.8, NH)
4{6,7}	1.31 (6H, d, ^3J 6.8, Me), 2.56 (3H, s, Me), 3.03 (1H, m, CH), 4.60 (2H, d, ^3J 5.8, CH_2), 7.21 (1H, m, H_{Py}-5), 7.34 (1H, d, ^3J 7.8, H_{Py}-3), 7.45 (4H, s, H_{Ar}), 7.70 (1H, t, ^3J 7.8, H_{Py}-4), 8.50 (1H, d, ^3J 4.9, H_{Py}-6), 8.90 t (1H, ^3J 5.8, NH)
4{12,7}	2.38 (3H, s, Me), 3.84 (3H, s, MeO), 4.60 (2H, d, ^3J 5.8, CH_2), 7.15 (1H, dt, ^3J 7.8, ^4J 1.0, H_{Ar}-4), 7.22 (1H, dd, ^3J 7.8, ^3J 4.9, H_{Py}-5), 7.27 (1H, d, ^3J 7.8, H_{Py}-3), 7.37 (2H, m, H_{Ar}-3,4), 7.57 (1H, td, ^3J 8.8, ^4J 1.0, H_{Ar}-6), 7.70 (1H, dt, ^3J 7.8,^4J 2.0, H_{Py}-4), 8.50 (1H, d, ^3J 4.9, Py H_{Py}-6), 8.90 (1H, t, ^3J 5.8, NH)
4{1,8}	2.57 (3H, s, Me), 4.49 (2H, d, ^3J 5.8, CH_2), 7.27 (1H, dd, ^3J 7.8, ^3J 4.9, H_{Py}-5), 7.55 (2H, dd, ^3J 7.8, ^4J 2.0, H_{Ph}-2,6), 7.57−7.64 (3H, m, H_{Ph}-3,4,5), 7.74 (1H, dd, ^3J 7.8, ^4J 2.0, H_{Py}-4), 8.40 (1H, d, ^3J 4.9, Py H_{Py}-6), 8.55 (1H, d, ^4J 2.0, H_{Py}-2), 9.15 (1H, t, ^3J 5.8, NH)
4{2,8}	2.03 (3H, s, Me), 2.37 (3H, s, Me), 4.50 (2H, d, ^3J 5.8, CH_2), 7.29 (1H, dd, ^3J 7.8, ^3J 4.9, H_{Py}-5), 7.31 (1H, d, ^3J 7.8, H_{Ar}-3), 7.42 (1H, t, ^3J 7.8, H_{Ar}-4), 7.45−7.54 (2H, m, H_{Ar}-5,6), 7.76 (1H, d, ^3J 7.8, H_{Py}-4), 8.41 (1H, d, ^3J 4.9, H_{Py}-6), 8.56 (1H, s, H_{Py}-2), 9.15 (1H, t, ^3J 5.8, NH)
4{8,8}	2.59 (3H, s, Me), 4.49 (2H, d, ^3J 5.8, CH_2), 7.28 (1H, dd, ^3J 7.8, ^3J 4.9, H_{Py}-5), 7.55 (1H, d, ^3J 6.8, H_{Ar}-4), 7.62 (2H, m, H_{Ar}-5,6), 7.67 (1H, s, H_{Ar}-2), 7.74 (1H, d, ^3J 7.8, H_{Py}-4), 8.40 (1H, d, ^3J 4.9, H_{Py}-6), 8.55 (1H, s, H_{Py}-2), 9.15 (1H, br.s, NH)
4{10,8}	2.56 (3H, s, Me), 4.49 (2H, d, ^3J 5.8, CH_2), 7.28 (1H, dd, ^3J 7.8, ^3J 4.9, H_{Py}-5), 7.38 (2H, t, ^3J 7.8, H_{Ar}-3,5), 7.62 (2H, dd, ^3J 8.8, ^3J 4.9, H_{Ar}-2,6), 7.74 (1H, d, ^3J 7.8, H_{Py}-4), 8.40 (1H, d, ^3J 4.9, H_{Py}-6), 8.55 (1H, s, H_{Py}-2), 9.14 (1H, t, ^3J 5.8, NH)

ably proceeded in a cascade manner involving a sequence of chemical transformations.

Conclusion

Elaborated multicomponent reaction provided the formation of large collections of triazole derivatives from commercially available components. It made possible to produce compounds with the diversity of substituents needed for discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques.

Experimental Section

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C, DMSO-d_6 as solvent). The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Amines **3** are commercially available, amine **3**{6} was synthesized according to the literature procedure.[26] Azides **1**{1−15} were prepared from corresponding amines.[27]

General Procedure for the Synthesis of Amides 4. An appropriate amine **3** (10.0 mmol), arylazide **1** (10.0 mmol), and triethylamine 1.4 mL were added to the solution of diketene (10.0 mmol) in dry acetonitrile (20 mL). The mixture was heated under reflux during 30 min. Then, it was cooled to room temperature, and the solid started to sediment.

Table 3. ^{13}C NMR Spectra of Amides **4**

	^{13}C NMR δ (ppm), recorded in DMSO-d_6					
product	CH_3	4-C_{Tr}	5-C_{Tr}	CO	aryl fragment	amine fragment
4{1,1}	10.0	138.9	137.1	161.0	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.0 (C_{Ph})	24.2 (2 × CH_2), 32.7 (2 × CH_2), 50.7 (C)
4{5,1}	10.0	138.9	137.0	161.0	14.4 (CH_3), 22.4 (CH_2), 33.6 (CH_2), 35.1 (CH_2), 125.9 (2 × CH_{Ar}), 130.1 (2 × CH_{Ar}), 133.8 (C_{Ar}), 145.1(C_{Ar})	24.2 (2 × CH_2), 32.7 (2 × CH_2), 50.7 (C)
4{10,1}	10.1	138.8	137.3	161.1	122.3 (CH_{Ar}), 125.9 (CH_{Ar}), 129.4 (CH_{Ar}), 132.4 (CH_{Ar}), 134.7 (C_{Ar}), 140.1 (C_{Ar})	24.2 (2 × CH_2), 32.7 (2 × CH_2), 50.5 (C)
4{1,2}	10.0	138.8	137.3	161.1	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.1 (C_{Ph})	25.7 (CH_2), 29.2 (CH_2), 43.0 (CH_2N), 67.8 (CH_2), 77.6 (CH)
4{9,2}	9.3	138.7	138.3	161.2	129.4 (CH_{Ar}), 130.4 (CH_{Ar}), 131.1 (CH_{Ar}), 131.2 (CH_{Ar}), 133.2 (C_{Ar}), 133.4 (C_{Ar})	25.7 (CH_2), 29.2 (CH_2), 43.0 (CH_2N), 67.8 (CH_2), 77.6 (CH)
4{11,2}	10.0	138.8	137.4	161.3	97.3 (C_{Ar}), 128.0 (2 × CH_{Ar}), 135.7 (C_{Ar}), 139.2 (2 × CH_{Ar})	25.8 (CH_2), 29.2 (CH_2), 43.0 (CH_2N), 67.8 (CH_2), 77.6 (CH)
4{15,2}	10.0	138.8	137.4	161.3	10.4 (CH_3), 22.4 (CH_2), 70.0 (CH_2O), 114.7 (2 × CH_{Ar}), 127.2 (2 × CH_{Ar}), 133.4 (C_{Ar}), 156.7 (C_{Ar})	25.8 (CH_2), 29.2 (CH_2), 43.0 (CH_2N), 67.8 (CH_2), 77.6 (CH)
4{1,3}	10.0	138.8	137.5	161.3	126.0 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.2 (C_{Ph})	29.4 (2 × CH_3), 35.2 (2 × CH_3), 42.1 (CH), 44.7 (2 × C), 51.2 (2 × CH_2)
4{12,3}	9.3	138.7	138.3	160.6	56.6 (CH_3O), 113.5 (CH_{Ar}), 121.6 (CH_{Ar}), 124.2 (CH_{Ar}), 129.5 (CH_{Ar}), 132.9 (C_{Ar}), 154.3 (C_{Ar})	29.4 (2 × CH_3), 35.2 (2 × CH_3), 42.1 (CH), 44.7 (2 × C), 51.2 (2 × CH_2)
4{13,3}	10.0	138.8	137.4	161.2	56.3 (MeO), 111.8 (CH_{Ar}), 116.4 (CH_{Ar}), 118.2 (CH_{Ar}), 131.2 (CH_{Ar}), 137.0 (C_{Ar}), 160.6 (C_{Ar})	29.4 (2 × CH_3), 35.2 (2 × CH_3), 42.1 (CH), 44.7 (2 × C), 51.2 (2 × CH_2)
4{1,4}	10.1	139.0	138.1	159.8	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.0 (C_{Ph})	64.6 (CH_2), 64.8 (CH_2), 110.2 (CH), 114.4 (CH), 117.3 (CH), 132.9 (C), 140.3 (C), 143.4 (C)
4{1,5}	10.0	138.7	137.4	161.3	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.0 (C_{Ph})	30.1 (CH_2), 39.7 (CH_2), 124.7 (CH), 125.8 (CH), 127.6 (CH), 142.2 (C)
4{4,5}	10.0	138.7	137.3	161.4	21.0 (CH_3), 126.0 (2 × CH_{Ar}), 130.3 (2 × CH_{Ar}), 133.9 (C_{Ar}), 143.1 (C_{Ar})	30.0 (CH_2), 39.7 (CH_2), 124.7 (CH), 125.8 (CH), 127.6 (CH), 142.2 (C)
4{13,5}	10.0	138.7	137.4	161.4	56.3 (MeO), 111.8 (CH_{Ar}), 116.4 (CH_{Ar}), 118.2 (CH_{Ar}), 131.2 (CH_{Ar}), 137.0 (C_{Ar}), 160.6 (C_{Ar})	30.0 (CH_2), 39.7 (CH_2), 124.7 (CH), 125.8 (CH), 127.6 (CH), 142.2 (C)
4{14,5}	10.0	138.6	137.6	161.3	55.6 (CH_3O), 114.1 (2 × CH_{Ar}), 123.9 (2 × CH_{Ar}), 131.7 (C_{Ar}), 157.7 (C_{Ar})	30.0 (CH_2), 39.7 (CH_2), 124.7 (CH), 125.8 (CH), 127.6 (CH), 142.2 (C)
4{1,6}	9.9	138.7	137.4	161.4	126.1 (2 × CH_{Ph}), 130.5 (2 × CH_{Ph}), 130.6 (CH_{Ph}), 135.8 (C_{Ph})	29.2 (CH_2), 46.1 (CH), 51.7 (CH_2), 55.3 (CH_2)
4{4,6}	10.0	138.7	137.4	161.4	21.0 (CH_3), 126.0 (2 × CH_{Ar}), 130.3 (2 × CH_{Ar}), 134.0 (C_{Ar}), 143.2 (C_{Ar})	29.2 (CH_2), 46.1 (CH), 51.7 (CH_2), 55.3 (CH_2)
4{7,6}	9.3	139.2	138.1	161.1	117.7 (d, $^2J_{CF}$ 19.1 Hz, CH_{Ar}), 123.3 (d, $^2J_{CF}$ 13.1 Hz, C_{Ar}), 126.3 (d, $^3J_{CF}$ 3.0 Hz, C_{Ar}), 129.8 (CH), 133.8 (d, $^3J_{CF}$ 8.0 Hz, C_{Ar}), 156.5 (d, $^1J_{CF}$ 250 Hz, C_{Ar})	29.2 (CH_2), 46.1 (CH), 51.7 (CH_2), 55.3 (CH_2)
4{8,6}	9.9	138.3	138.1	161.3	117.3 (d, $^2J_{CF}$ 23.2 Hz, 2 × CH_{Ar}), 128.6 (d, $^3J_{CF}$ 9.1 Hz, 2 × CH_{Ar}), 122.3 (C_{Ar}), 163.2 (d, $^1J_{CF}$ 247.7 Hz, C_{Ar})	29.2 (CH_2), 46.1 (CH), 51.7 (CH_2), 55.3 (CH_2)
4{1,7}	10.0	138.6	137.4	161.7	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 136.1 (C_{Ph})	44.5 (CH_2), 122.7 (CH_{Py}), 123.1 (CH_{Py}), 136.0 (CH_{Py}), 149.5 (CH_{Py}), 159.1 (C_{Py})
4{2,7}	9.4	138.1	138.2	161.6	17.4 (CH_3), 127.8 (CH_{Ar}), 128.0 (CH_{Ar}), 131.1 (C_{Ar}), 132.0 (CH_{Ar}), 135.7 (C_{Ar}), 135.9 (CH_{Ar})	44.5 (CH_2), 122.7 (CH_{Py}), 123.1 (CH_{Py}), 136.0 (CH_{Py}), 149.5 (CH_{Py}), 159.1 (C_{Py})
4{3,7}	10.0	138.6	137.4	161.7	21.4 (CH_3), 121.5 (CH_{Ar}), 126.4 (CH_{Ar}), 130.1 (CH_{Ar}), 131.2 (CH_{Ar}), 137.4 (C_{Ar}), 140.2 (C_{Ar})	44.5 (CH_2), 122.7 (CH_{Py}), 123.1 (CH_{Py}), 136.0 (CH_{Py}), 149.5 (CH_{Py}), 159.1 (C_{Py})
4{6,7}	10.0	138.6	137.4	161.7	24.8 (CH_3), 33.6 (CH), 126.0 (2 × CH_{Ar}), 127.7 (2 × CH_{Ar}), 140.2 (C_{Ar}), 143.4 (C_{Ar})	44.5 (CH_2), 122.7 (CH_{Py}), 123.1 (CH_{Py}), 136.0 (CH_{Py}), 149.5 (CH_{Py}), 159.1 (C_{Py})
4{12,7}	9.3	138.7	138.3	160.6	56.6 (CH_3O), 113.5 (CH_{Ar}), 121.6 (CH_{Ar}), 124.2 (CH_{Ar}), 129.5 (CH_{Ar}), 132.9 (C_{Ar}), 154.3 (C_{Ar})	44.5 (CH_2), 122.7 (CH_{Py}), 123.1 (CH_{Py}), 136.0 (CH_{Py}), 149.5 (CH_{Py}), 159.1 (C_{Py})
4{1,8}	10.0	138.6	137.4	161.7	126.1 (2 × CH_{Ph}), 130.4 (2 × CH_{Ph}), 130.7 (CH_{Ph}), 135.9 (C_{Ph})	39.7 (CH_2), 124.4 (CH_{Py}), 134.9 (CH_{Py}), 136.0 (C_{Py}), 148.7(CH_{Py}), 149.7 (CH_{Py})
4{2,8}	9.4	138.2	138.2	161.6	17.4 (CH_3), 127.8 (CH_{Ar}), 128.0 (CH_{Ar}), 131.1 (C_{Ar}), 132.0 (CH_{Ar}), 135.7 (C_{Ar}), 135.9 (CH_{Ar})	39.7 (CH_2), 124.4 (CH_{Py}), 134.9 (CH_{Py}), 136.0 (C_{Py}), 148.7(CH_{Py}), 149.7 (CH_{Py})
4{8,8}	10.0	138.6	137.4	161.7	122.3 (CH_{Ar}), 125.8 (CH_{Ar}), 129.4 (CH_{Ar}), 132.5 (CH_{Ar}), 134.7 (C_{Ar}), 140.0 (C_{Ar})	39.7 (CH_2), 124.4 (CH_{Py}), 134.9 (CH_{Py}), 136.0 (C_{Py}), 148.7(CH_{Py}), 149.7 (CH_{Py})
4{10,8}	9.9	138.3	138.1	161.3	117.3 (d, $^2J_{CF}$ 23.2 Hz, 2 × CH_{Ar}), 128.6 (d, $^3J_{CF}$ 9.1 Hz, 2 × CH_{Ar}), 122.3 (C_{Ar}), 163.2 (d, $^1J_{CF}$ 247.7 Hz, C_{Ar})	39.7 (CH_2), 124.4 (CH_{Py}), 134.9 (CH_{Py}), 136.0 (C_{Py}), 148.7(CH_{Py}), 149.7 (CH_{Py})

The product was filtered and washed with methanol to give triazole **3** as a white solid. When the amide was well soluble in acetonitrile, water was added dropwise until the solid started to appear. See Table 1 for analytical data of **4**, Table 2 for their ^{1}H NMR spetra, and Table 3 for the ^{13}C NMR data.

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CC900012W