ORGANIC LETTERS

2012
Vol. 14, No. 7
1804–1807

Cascade Intermolecular Michael Addition–Intramolecular Azide/Internal Alkyne 1,3-Dipolar Cycloaddition Reaction in One Pot

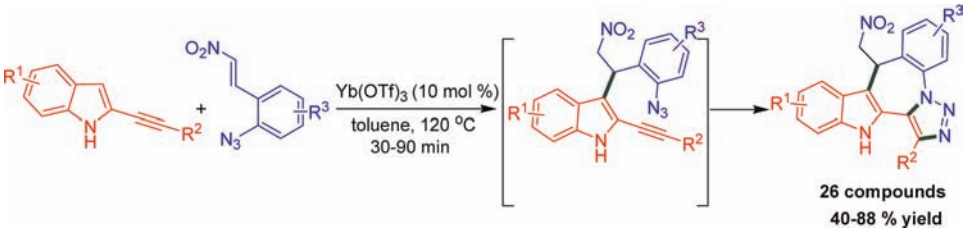
Rajesh K. Arigela,[†] Anil K. Mandadapu,[†] Sudhir K. Sharma,[†] Brijesh Kumar,[‡] and Bijoy Kundu*[,†]

Medicinal & Process Chemistry Division and Sophisticated Analytical and Instrumental Facility, Central Drug Research Institute, CSIR, Lucknow-226001, India

bijoy_kundu@yahoo.com; b_kundu@cdri.res.in

Received February 17, 2012

ABSTRACT



A rapid one-pot protocol for the synthesis of indole-based polyheterocycles via a sequential Lewis acid catalyzed intermolecular Michael addition and an intramolecular azide/internal alkyne 1,3-dipolar cycloaddition reaction has been described. The generality of the method has been demonstrated by treating a series of aromatic/aliphatic 2-alkynyl indoles with substituted (*E*)-1-azido-2-(2-nitrovinyl)benzenes to furnish annulated tetracyclic indolo[2,3-*c*][1,2,3]triazolo[1,5-*a*][1]benzazepines in good yields.

The intermolecular azide–alkyne 1,3-dipolar cycloaddition reaction has remained one of the classical methods for the synthesis of 1,2,3-triazoles with widespread applications in medicinal chemistry, chemical biology, and material science.[1] The ease and efficacy of the reaction has been successfully demonstrated in both aqueous[2] and organic solvents involving either metal-catalyzed[3] or metal-free conditions[4] with temperatures ranging from ambient to heating. Besides, the remarkable cycloaddition process was found to be compatible with both terminal/internal

[†] Medicinal & Process Chemistry Division.
[‡] Sophisticated Analytical and Instrumental Facility.

(1) (a) Mamat, C.; Ramenda, T.; Wuest, F. R. *Mini-Rev. Org. Chem.* **2009**, *6*, 21–34. (b) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13–21. (c) Wangler, C.; Schirrmacher, R.; Bartenstein, P.; Wangler, B. *Curr. Med. Chem.* **2010**, *17*, 1092–1160. (d) Walsh, J. C.; Kolb, H. C. *Chimia (Aarau)* **2010**, *64*, 29–33. (e) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15–54. (f) Kou, L.; He, H.; Gao, C. *Nano-Micro Lett.* **2010**, *2*, 177–183. (g) Kou, L.; He, H.; Gao, C. *Macromol. Rapid Commun.* **2008**, *29*, 1073–1089. (h) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. (i) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68. (j) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015. (k) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207–4220. (l) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2010**, *39*, 2522–2544.

(2) (a) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Synlett* **2007**, 1591–1594. (b) Li, P.; Wang, L. *Lett. Org. Chem.* **2007**, *4*, 23–26. (c) Kumar, I.; Rode, C. V. *Chem. Lett.* **2007**, *36*, 592–593. (d) Zhao, Y. B.; Yan, Z. Y.; Liang, Y. M. *Tetrahedron Lett.* **2006**, *47*, 1545–1549. (e) Reddy, K. R.; Rajgopal, K.; Kantam, M. L. *Synlett* **2006**, 957–959. (f) Wang, Z. X.; Zhao, Z. G. *J. Heterocycl. Chem.* **2007**, *44*, 89–92. (g) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Adv. Synth. Catal.* **2010**, *352*, 3208–3214. (h) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *J. Org. Chem.* **2011**, *76*, 8394–8405. (i) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Heterocycles* **2012**, *84*, 1033–1044.

(3) (a) Eun, J. Y.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520–5528. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999. (d) Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 7558–7564. (e) Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475–9492.

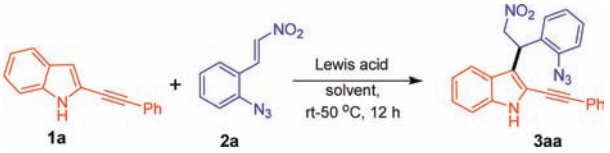
(4) (a) Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4217–4219. (b) Qin, A.; Jim, C. K. W.; Lu, W.; Lam, J. W. Y.; Haeussler, M.; Dong, Y.; Sung, H. H. Y.; Williams, I. D.; Wong, G. K. L.; Tang, B. Z. *Macromolecules* **2007**, *40*, 2308–2317. (c) For review: Becer, C. R; Hoogenboom, R; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900–4908. (d) Li, P.; Wang, L. *Lett. Org. Chem.* **2007**, *4*, 23–26. (e) Li, R.; Jansen, D. J.; Datta, A. *Org. Biomol. Chem.* **2009**, *7*, 1921–1930.

10.1021/ol300399y
Published on Web 03/22/2012

alkynes and diynes[5] resulting in triazoles with a high order of regioselectivity. In addition to this intermolecular azide–alkyne 1,3-dipolar cycloaddition format, several groups have also applied the intramolecular azide–alkyne 1,3-dipolar cycloaddition strategy for the synthesis of triazole linked amino acids/oligopeptides[6] and triazole-annulated polyheterocycles.[7] However, most of these intramolecular strategies predominantly involved terminal alkynes in a multistep format[8] to promote 1,3-dipolar cycloaddition with limited applications[9] to internal alkynes. Ideally, an intramolecular 1,3-dipolar cycloaddition reaction in contrast to the intermolecular format can be expected to furnish two annulated cyclic rings[10] including a triazole ring in a single step and can thus be considered as a useful strategy for generating molecular complexity in a one-pot format. In our laboratory we had been exploiting the nucleophilicities of the three N-1, C-3, and C-2 positions in the indole by treating functionalized indoles with alkynyl (electrophiles) components to access annulated indoles, fused at either of the two positions using one-pot strategies.[11] In one-pot formats functionalized indoles, in general, have remained relatively underexplored.[12] In continuation, we next directed our effort to yet another class of functionalized indoles, i.e. 2-alkynyl-indoles, that will act as a combined source for both indole (nucleophile) and an alkyne (electrophile) moiety for the development of a one-pot strategy for the synthesis of annulated indoles involving an intramolecular 1,3-dipolar cycloaddition reaction. To achieve this, we envisaged that functionalizing position C-3 in the 2-alkynyl-indole with an azido arene moiety may enforce (due to the close proximity of the azide and the alkyne moieties) the formation of two annulated 7- and 5-membered heterocyclic rings *via* the intramolecular 1,3-dipolar cycloaddition reaction in a single step. Here, we report a fast and versatile one-pot cascade intermolecular Michael addition-intramolecular azide-internal alkyne 1,3-dipolar cycloaddition reaction to furnish annulated tetracyclic indolo[2,3-*c*]-[1,2,3]triazolo[1,5-*a*][1]benzazepines in good yields.

Our studies commenced with the development of a methodology for the C-3 functionalization of 2-phenyl-

Table 1. Optimization for the Synthesis of C-3 Alkylated Product **3aa**



entry	catalyst	solvent	temp	yield (%) of **3aa**
1	$Yb(OTf)_3$	toluene	rt	10[b]
2	–[c]	toluene	rt	NR
3	$Yb(OTf)_3$	MeCN	rt	61[a]
4	$Yb(OTf)_3$	DMF	rt	NR
5	$Sc(OTf)_3$	MeCN	rt	NR
6	$Zn(OTf)_2$	MeCN	rt	NR
7	AgOTf	MeCN	rt	NR
8	$Hg(OAc)_2$	MeCN	rt	NR
9	$Cu(OTf)_2$	MeCN	rt	<10[b]
10	$Sc(OTf)_3$	MeCN	50 °C	55

[a] Isolated yields. [b] Yields based on HPLC (C18 reversed-phase column; 150 mm × 4.6 mm; 5 μm). [c] Reaction carried out without catalyst; NR = No Reaction. All reactions were carried out on a 1 mmol scale with 10 mol % of Lewis acid in 5 mL of solvent at rt and monitored for 12 h.

ethynyl-1*H*-indole **1a** by treating it with a (*E*)-1-azido-2-(2-nitrovinyl)benzene **2a**. Among several methods described in the literature[13] for the C-3 functionalization of the indoles under mild conditions, we proposed to use a Lewis acid catalyzed Michael addition, and the results have been summarized in Table 1. Accordingly, **1a** was initially treated with **2a** in the presence of $Yb(OTf)_3$ in toluene at rt, and after 12 h of stirring a new product was obtained in ~10% isolated yield with a molecular weight of 407 Da (entry 1). The structure of the product was elucidated by the combined use of ^1H and ^{13}C NMR experiments that led to its identification as 3-[1-(2-azido-phenyl)-2-nitro-ethyl]-2-phenylethynyl-1*H*-indole **3aa** arising from the C-3 alkylation of the indole. Carrying out the same reaction in the absence of catalyst failed to yield **3aa** (entry 2). Switching the solvent from toluene to acetonitrile at rt in the presence of $Yb(OTf)_3$ furnished **3aa** in 61% isolated yield (entry 3), whereas carrying out the reaction in DMF at rt failed to

(5) (a) Mandadapu, A. K.; Sharma, S. K.; Gupta, S.; Krishna, D. G. V.; Kundu, B. *Org. Lett.* **2011**, *13*, 3162–3165. (b) Monkowius, U.; Ritter, S.; Konig, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, 4597–4606. (c) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Quarta, M. R.; Fittipaldi, M. *Synthesis* **2009**, 3853–3859. (d) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573–10580. (e) Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Aizpurua, M. S.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584–1587.

(6) (a) Sai Sudhir, V.; Nasir Baig, R. B.; Chandrasekaran, S. *Eur. J. Org. Chem.* **2008**, 2423–2429. (b) Turner, R. A.; Oliver, A. G.; Scott Lokey, R. *Org. Lett.* **2007**, *9*, 5011–5014.

(7) (a) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 3725–3728. (b) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439–8441.

(8) (a) Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 8639–8643. (b) Majumdar, K. C.; Ray, K.; Ganai, S. *Synthesis* **2010**, 2101–2105.

(9) For a recent review: Majumdar, K. C.; Ray, K. *Synthesis* **2011**, 3767–3783.

(10) Kunick, C. *Liebigs Ann. Chem.* **1993**, *10*, 1141–1143.

(11) (a) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 6022–6024. (b) Sharma, S. K.; Gupta, S.; Saifuddin, M.; Mandadapu, A. K.; Agarwal, P. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2011**, *52*, 65–68. (c) Gupta, S.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10154–10162. (d) Gupta, S.; Sharma, S. K.; Mandadapu, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2011**, *52*, 4288–4291. (e) Sharma, S. K.; Mandadapu, A. K.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 6798–6805.

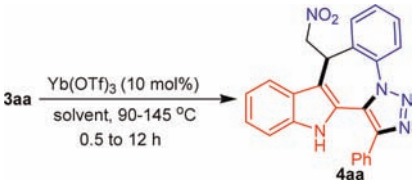
(12) For review, see: Sapi, J.; Laronze, J. Y. *ARKIVOC* **2004**, 208–222 and references cited therein.

(13) (a) Takayoshi, A.; Makiko, W.; Naota, Y. *J. Org. Chem.* **2011**, *76*, 2909–2912. (b) Epifano, F.; Genovese, S.; Rosati, O.; Tagliapietra, S.; Pelucchini, C.; Curini, M. *Tetrahedron Lett.* **2011**, *52*, 568–571. (c) Young, K. H.; Sungkyung, K.; Kyungsoo, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 4476–4478. (d) Jianwei, X.; Xinhai, Z.; Manna, H.; Fei, M.; Man, W; Yiqian, W. *Synth. Commun.* **2010**, *40*, 3259–3267.

yield any product (entry 4). Replacement of $Yb(OTf)_3$ with other Lewis acid catalysts $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, AgOTf, and $Hg(OAc)_2$ played a detrimental role in the reaction (entries 5–9). However, carrying out the reaction in the presence of $Sc(OTf)_3$ at 50 °C in MeCN furnished **3aa** in 55% isolated yield (entry 10).

Next we examined the ability of intermediate **3aa** to undergo an intramolecular azide-internal alkyne 1,3-dipolar cycloaddition reaction, and the results have been summarized in Table 2. For this **3aa** was subjected to heating in toluene under reflux in the presence of $Yb(OTf)_3$, and to our delight within 30 min we obtained an annulated

Table 2. Optimization for the Conversion of **3aa** to **4aa**



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[a] of **4aa**
1	$Yb(OTf)_3$	toluene	120	0.5	88
2	–[b]	toluene	120	0.5	90
3	$Yb(OTf)_3$	MeCN	90	12	52
4	–[b]	MeCN	90	12	45
5	$Yb(OTf)_3$	tylene	145	0.5	85
6	–[b]	xylene	145	0.5	86

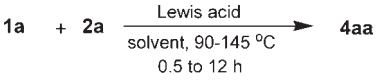
[a] Isolated yields. [b] Reaction carried out without catalyst.

tetracyclic compound **4aa** comprising a benzazepine ring and a triazole ring annulated to the indole in 88% isolated yield (entry 1).

In order to establish the role of $Yb(OTf)_3$ in the 1,3-dipolar cycloaddition reaction, we carried out the same reaction in the absence of catalyst and gratifyingly product **4aa** was isolated in 90% yield (entry 2). Switching the solvent from toluene to acetonitrile in both the presence and absence of $Yb(OTf)_3$ furnished **4aa** (entries 3 and 4) in reduced yield. However carrying out the reaction in xylene had no effect on the yield of **4aa** (entries 5 and 6). From the above studies it is apparent that while the Lewis acid played a crucial role in the C-3 functionalization of the indole for introducing azido arenes to furnish **3aa**, the intramolecular 1,3-dipolar cycloaddition occurred without the involvement of the catalyst and remained a thermally induced reaction.

Once the reaction conditions for the synthesis of **3aa** and **4aa** were optimized, we proceeded with the development of a one-pot strategy for the synthesis of **4aa** from **1a** and **2a**, and the results have been summarized in Table 3. We commenced our studies by treating **1a** with **2a** in toluene under reflux in the absence of a Lewis acid, which failed to yield the desired product (entry 1). Carrying out the reaction in the presence of $Yb(OTf)_3$ using toluene as solvent under reflux afforded **4aa** within 30 min in 86% isolated yield (entry 2). Switching the solvent from toluene to acetonitrile and heating at 90 °C furnished a mixture of **3aa** and **4aa** in 14% and 42% yields (entry 3), whereas in xylene at 145 °C **4aa** was furnished in 38% yield (entry 4). Carrying out the reaction in DMF and heating at 120 °C failed to furnish **4aa**; instead **3aa** was obatined in 45% isolated yield (entry 5). Replacing $Yb(OTf)_3$ with other Lewis acids resulted in only $Sc(OTf)_3$ and $Zn(OTf)_2$ furnishing **4aa** in 58% (entry 6) and 35% isolated yield (entry 7); AgOTf, $Cu(OTf)_2$, and $Hg(OAc)_2$ failed to even promote the formation of **3aa** and **4aa** (entries 8–10).

Table 3. Optimization of Reaction Conditions for the One-Pot Synthesis of **4aa**

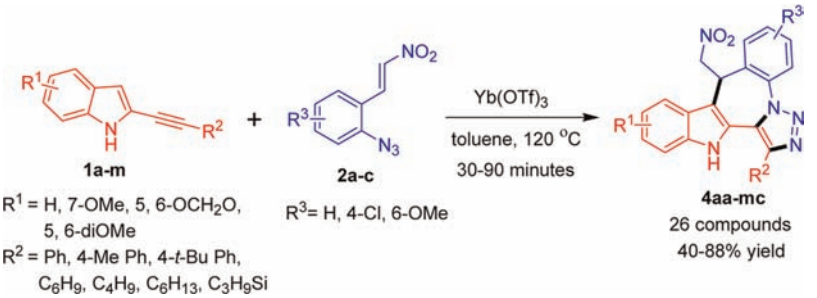


entry	catalyst	solvent	temp (°C)	time (h)	yield (%) of **3aa/4aa**
1	–[b]	toluene	120	0.5	NR
2	$Yb(OTf)_3$	toluene	120	12	0/86[a]
3	$Yb(OTf)_3$	MeCN	90	12	14/42[c]
4	$Yb(OTf)_3$	xylene	145	12	0/38[a]
5	$Yb(OTf)_3$	DMF	120	12	45[a]/0
6	$Sc(OTf)_3$	toluene	120	12	0/58[a]
7	$Zn(OTf)_2$	toluene	120	12	0/35[a]
8	AgOTf	toluene	120	12	NR
9	$Cu(OTf)_2$	toluene	120	12	NR
10	$Hg(OAc)_2$	toluene	120	12	NR

[a] Isolated yields. [b] Reaction carried out without catalyst. [c] Yields based on HPLC (C18 reversed-phase column; 150 mm × 4.6 mm; 5 μm). NR = No Reaction. All reactions were carried out on a 1 mmol scale with 10 mol % of Lewis acid in 5 mL of solvent.

Following the optimization of reaction conditions for the synthesis of indole-based tetracyclic **4aa** was established, the scope and limitation of the one-pot strategy was established by treating a variety of 2-alkynyl indoles with a range of preformed substituted (*E*)-1-azido-2-(2-nitrovinyl)benzenes. The R^1 in the aromatic ring of the indole has been substituted with 7-methoxy, 5,6-dimethoxy, and 5,6-methylenedioxy groups whereas R^2 in the alkyne included aliphatic, aromatic, and trimethylsilyl moieties. The R^3 in the aromatic ring of the nitrostyrene has been substituted by a 4-chloro as well as a 6-methoxy group. In all, 26 compounds based on **4aa**–**mc** were synthesized in isolated yields of 40–88% (Table 4), and in all cases, the one-pot reactions were found to be complete with 30–90 min. As is evident from Table 4, the electronic properties of the substituent on the phenyl ring of the indole moiety or nitrostyrene had no effect on the yields of the final compounds. Similarly, replacing R^2 with an aliphatic moiety or an aromatic ring had a negligible effect on the reactions, offering products with

Table 4. One-Pot Synthesis of Tetracyclic Compounds Based on **4**[a]



no.	R^1	R^2	R^3	time (min)	product	% yield
1	H	C_6H_5	H	30	**4aa**	86
2	H	4-CH_3-C_6H_4	H	35	**4ba**	85
3	H	4-*t*-Bu-C_6H_4	H	30	**4ca**	84
4	H	C_6H_9	H	40	**4ea**	80
5	H	C_6H_5	11-Cl	30	**4ab**	86
6	H	4-CH_3-C_6H_4	11-Cl	35	**4bb**	80
7	H	4-*t*-Bu-C_6H_4	11-Cl	35	**4cb**	83
8	H	C_6H_9	11-Cl	40	**4eb**	78
9	H	C_6H_5	13-CH_3O	30	**4ac**	88
10	H	4-*t*-Bu-C_6H_4	13-CH_3O	35	**4cc**	85
11	H	C_6H_9	13-CH_3O	45	**4ec**	83
12	H	C_6H_{13}	13-CH_3O	45	**4dc**	82
13	5-CH_3O	C_6H_5	11-Cl	30	**4kb**	80
14	5-CH_3O	C_6H_5	13-CH_3O	35	**4kc**	84
15	5-CH_3O	C_4H_9	H	45	**4la**	79
16	5-CH_3O	C_4H_9	13-CH_3O	40	**4lc**	78
17	6,7-di-CH_3O	C_6H_5	H	35	**4fa**	81
18	6,7-di-CH_3O	4-CH_3-C_6H_4	H	35	**4ga**	77
19	6,7-di-CH_3O	C_6H_5	11-Cl	40	**4fb**	80
20	6,7-di-CH_3O	4-CH_3-C_6H_4	11-Cl	45	**4gb**	82
21	6,7-di-CH_3O	C_6H_9	H	40	**4ha**	76
22	6,7-OCH_2O-	C_6H_5	H	35	**4ia**	82
23	6,7-OCH_2O-	C_6H_5	13-CH_3O	40	**4ic**	84
24	6,7-OCH_2O-	C_6H_9	H	45	**4ja**	77
25	H	H	H	90	**4ma**	40
26	H	H	13-CH_3O	90	**4mc**	42

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and $Yb(OTf)_3$ (0.1 mmol) in toluene (5 mL) at 120 °C under N_2 atmosphere.

minimal variation in yields. However, substituting R^2 with a trimethyl silyl group furnished **4ma** (R^2 = H) and **4mc** (R^2 = H) in reduced yields of 40 and 42% respectively. In general, internal alkynes with R^2 as the aromatic ring furnished products in 77−88% isolated yield, whereas R^2 having an aliphatic and trimethyl silyl moiety furnished products in 40−83% isolated yields.

In conclusion, we have developed a simple and efficient cascade reaction for the synthesis of highly substituted indolo[2,3-*c*][1,2,3]triazolo[1,5-*a*][1]benzazepines in good yields under mild reaction conditions. The salient feature of the protocol involves a Lewis acid catalyzed intermolecular Michael addition followed by a thermal induced intramolecular azide/internal alkyne 1,3-dipolar cycloaddition reaction in one pot. Further studies are in progress to extend this one-pot intramolecular azide/internal alkyne 1,3-dipolar cycloaddition strategy to other functionalized indoles, and findings shall be published elsewhere.

Acknowledgment. R.K.A., A.K.M., and S.K.S. are thankful to CSIR, New Delhi, India for financial support. The authors also would like to thank SAIF, CDRI, India for providing analytical data.

Supporting Information Available. Copies of ^1H, ^{13}C NMR spectra and HRMS of all final and starting compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.