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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7618–7623

A new organocatalyst for Friedel–Crafts alkylation of 2-naphthols with isatins: application of an organo-click strategy for the cascade synthesis of highly functionalized molecules

Dhevalapally B. Ramachary,* G. Babul Reddy and Rumpa Mondal

School of Chemistry, University of Hyderabad, Central University (PO), Hyderabad 500 046, India

Received 12 July 2007; revised 23 August 2007; accepted 30 August 2007
Available online 4 September 2007

Abstract—The three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions of 2-naphthols, substituted isatins and azides under dimethylamino-ethanol/Cu^{I}-catalysis furnished highly functionalized 1,4-disubstituted [1,2,3]-triazoles.
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1. Introduction

Catalytic Friedel–Crafts alkylation is a powerful synthetic method for the preparation of highly functionalized aromatic compounds via C–C and C–N bond formation, which can generate important classes of building blocks for pharmaceutically relevant compounds.[1] Due to its atom-economy, the direct catalytic Friedel–Crafts alkylation has received increasing attention.[2] Recently, MacMillan and Jørgensen developed asymmetric Friedel–Crafts alkylation and amination reactions of aromatic molecules with active olefins and electron-deficient substrates using simple chiral amines (organocatalysts) as asymmetric catalysts.[3] Nevertheless, this interesting class of organocatalysts have been used so far only for the following two types of Friedel–Crafts alkylation reactions: (1) the direct Friedel–Crafts alkylation of pyrroles with enals via Michael addition;[3a] and (2) amination of 2-naphthols with diethyl azodicarboxylates to furnish asymmetric non-biaryl atropisomers.[3b]

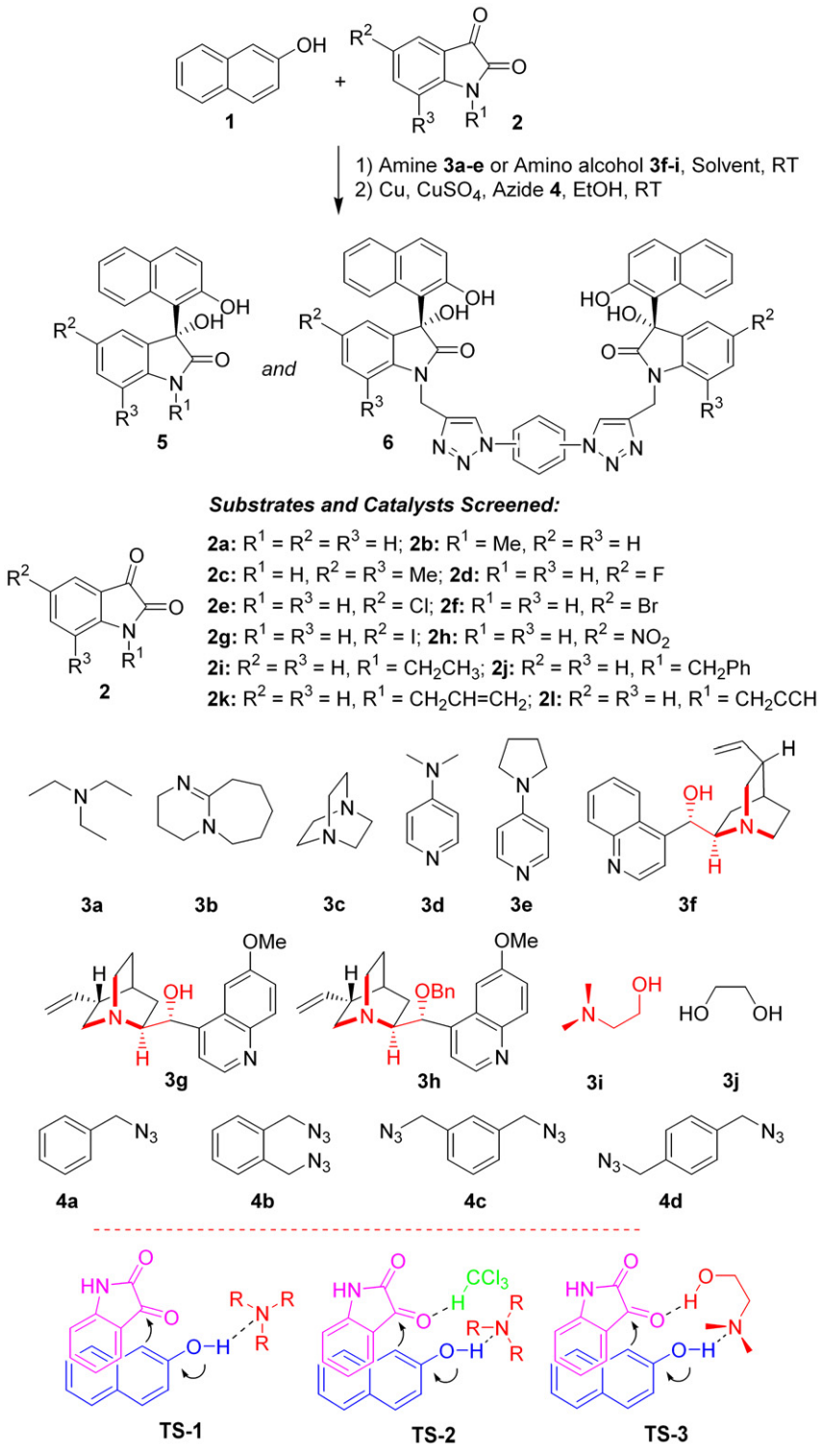
Chiral dialkylamino-ethanol derivatives (e.g., cinchona alkaloids) have been catalysts of choice for the activation of CH-acids and alcohols, leading to a number of asymmetric additions of various nucleophiles to electron-deficient substrates.[4] However, the chiral dialkylamino-ethanol derivatives were only investigated for catalysis of Michael type reactions of CH-acids with electron-deficient substrates.[4] We have now utilized dialkylamino-ethanol derivatives **3f–i** as catalysts for the Friedel–Crafts alkylation of 2-naphthols **1** with substituted isatins **2** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **5** in good yields as shown in Scheme 1. We have also developed organo-click,[5] three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions, which produce highly functionalized 1,2,3-triazoles **6** from 2-naphthol **1**, 1-prop-2-ynyl-1*H*-indole-2,3-dione **2l**, benzyl azide **4a** or bis-azido benzenes **4b–d**, catalyst **3i**, copper and copper sulfate as shown in Scheme 1.

3-Substituted-3-hydroxyindolin-2-ones **5** are important substrates for studying biological activity as well as useful synthetic intermediates for drug candidates and alkaloids. As a consequence, the development of practical methods for their preparation is of interest. The 3-substituted-3-hydroxyoxindole moiety is present in several pharmacologically active alkaloids such as celogentin K,[6] donaxaridine,[7] convolutamydines,[8] dioxibrassinine,[9] welwitindolinone C,[10] TMC-95s,[11] and 3′-hydroxyglucoisatisin,[12] in addition to several others.

The mechanistic proposal for the Lewis base-catalyzed Friedel–Crafts reaction of 2-naphthol **1** with isatins **2** in aprotic-nonpolar and protic-polar solvents indicates the involvement of **TS-1** and **TS-2**, respectively (Scheme 1). Interestingly, combination of a domino Lewis base and Brønsted acid-catalyzed Friedel–Crafts reaction of 2-naphthol **1** with isatins **2** in aprotic-nonpolar solvents indicates that **TS-3** is involved in the reaction. Thus, we

Keywords: Azides; Dimethylamino-ethanol; Friedel–Crafts alkylation; Organo-Click; Organocatalysis.
* Corresponding author. Tel.: +91 40 23134816; fax: +91 40 23012460; e-mail: ramsc@uohyd.ernet.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.129

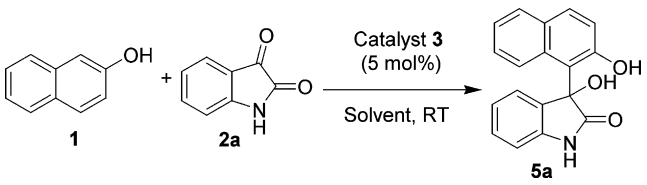


Scheme 1. Direct application of an organo-click strategy for the cascade synthesis of highly functionalized molecules.

speculated that simple dimethylamino-ethanol **3i** was capable potentially of promoting the direct Friedel–Crafts reaction via **TS-3**. Herein, we report our findings that a catalytic amount of dimethylamino-ethanol **3i** promoted the selective direct Friedel–Crafts alkylation of 2-naphthols **1** with substituted isatins **2** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **5** in high yields (Scheme 1).

The preliminary Friedel–Crafts alkylation (FCA) reaction between 2-naphthol **1** and isatin **2a** was carried out with 10 mol % of TEA **3a** as catalyst in $PhCH_3$. As expected, the reaction afforded product **5a** in 99% conversion and 90% yield after 24 h (via **TS-1**, Table 1, entry 1), which was purified by simple filtration followed by column chromatography. The rate of the **3a**-catalyzed FCA reaction was increased in $CHCl_3$

Table 1. Optimization of the organocatalytic Friedel–Crafts alkylation of 2-naphthol **1** with isatin **2a**[a]



Entry	Catalyst	Solvent	Time (h)	Conversion[a] (%)	Yield[b] (%)
1[c]	**3a**	$PhCH_3$	24	99	90
2[c]	**3a**	$CHCl_3$	9	99	92
3[c]	**3a**	CH_2Cl_2	9	99	90
4	**3b**	$PhCH_3$	24	—	—
5	**3c**	$PhCH_3$	24	70	60
6	**3d**	$PhCH_3$	24	80	75
7	**3e**	$PhCH_3$	10	99	96
8	**3f**	$PhCH_3$	6	99	97
9	**3g**	$PhCH_3$	8	99	94
10	**3h**	$PhCH_3$	24	70	60
11	**3i**	$PhCH_3$	5	99	96
12	**3i**	PhH	3	99	96
13	**3i**	CH_2Cl_2	5	99	96
14	**3i**	DMSO	24	20	10
15	**3j**	$PhCH_3$	24	5	<5
16	**3a/3j**	$PhCH_3$	8	99	96
17	—	$PhCH_3$	24	5	<5

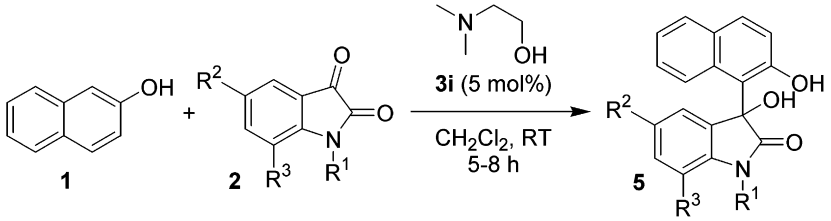
[a] Both reactants **1** and **2a** and catalyst **3** were mixed at the same time in solvent and stirred at room temperature; conversion based on TLC and ^{1}H NMR analysis.
[b] Yield refers to the column purified product.
[c] 10 mol % of triethyl-amine **3a** was used as catalyst.

and CH_2Cl_2 (entries 2 and 3). DBU **3b** did not catalyze the FCA reaction, however DABCO **3c** catalyzed the FCA reaction with 70% conversion after 24 h in $PhCH_3$ (entries 4 and 5). DMAP **3d** and 4-pyrrolidin-1-yl-pyridine **3e** catalyzed the FCA reaction of **1** and **2a** to furnish the expected product **5a** in 80% and 99% conversions after 24 and 10 h, respectively, in $PhCH_3$ (entries 6 and 7). Interestingly, the cinchona alkaloids, cinchonine **3f** and quinine **3g** catalyzed the FCA reaction in $PhCH_3$ to furnish **5a** with 99% conversion after 6–8 h as shown in Table 1, entries 8 and 9.[13] This unexpected, rapid FCA reaction with cinchonine **3f** and quinine **3g** can be explained by the involvement of both the amine and alcohol groups of **3f** and **3g** in the transition state. This was further confirmed by testing the FCA reaction of **1** and **2a** with alcohol protected quinine derivative **3h**, which required a longer reaction time to furnish the FCA adduct **5a** in $PhCH_3$ with 70% conversion (Table 1, entry 10).

Next, we investigated the same reaction with active dimethylamino-ethanol **3i** as catalyst (see Scheme 1). Interestingly, FCA reactions of **1** and **2a** with 5 mol % of **3i** in $PhCH_3$, PhH or CH_2Cl_2 at 25 °C for 3–5 h furnished the expected FCA adduct **5a** in 99% conversion and 96% yield (Table 1, entries 11–13). Dimethylamino-ethanol **3i** catalyzed the FCA reaction through **TS-3** as depicted in Scheme 1 and this was further confirmed by controlled experiments (Table 1, entries 14–17). The optimum conditions (entries 11 and 13) involved the use of 5 mol % of catalyst **3i** in $PhCH_3$ or CH_2Cl_2 at 25 °C.

After these interesting results, we decided to investigate the scope and limitations of the FCA reaction with a range of isatins **2a–l** using 5 mol % of **3i** as catalyst in CH_2Cl_2 at 25 °C (Table 2). Different 5-substituted

Table 2. Chemically diverse libraries of Friedel–Crafts alkylation products **5**



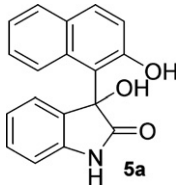
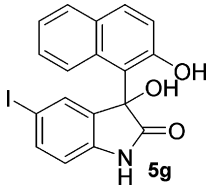
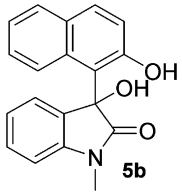
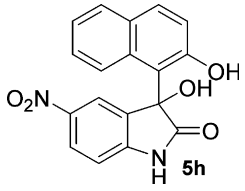
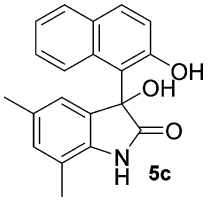
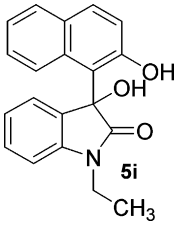
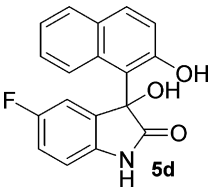
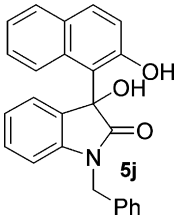
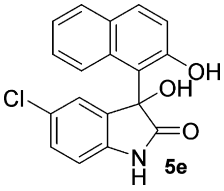
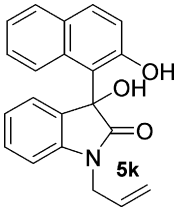
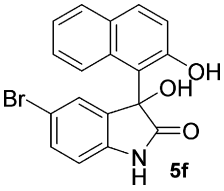
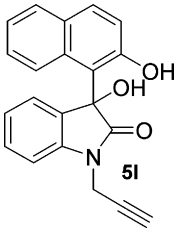
Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1	 **5a**	96	7	 **5g**	92
2	 **5b**	89	8	 **5h**	92

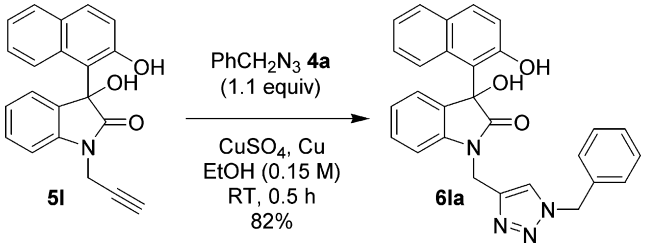
Table 2 (*continued*)

Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
3	 **5c**	89	9	 **5i**	91
4	 **5d**	94	10	 **5j**	92
5	 **5e**	93	11	 **5k**	94
6	 **5f**	92	12	 **5l**	92

[a] Yield refers to the column purified product.

isatins **2c**–**h** and 1-substituted isatins **2b**, **2i**–**l** furnished adducts **5a**–**l** in very good yields. Many of the products were purified by simple filtration to give 90–95% purity.

Huisgen 1,3-dipolar cycloadditions[14] are important processes. The cycloaddition of azides and alkynes to give triazoles is a very useful member of this family. Huisgen cycloaddition of propargyl substituted, 3-hydroxy-3-(2-hydroxynaphthalen-1-yl)-1-prop-2-ynyl-1,3-dihydroindol-2-one **5l** with benzyl azide **4a** under $CuSO_4$/Cu catalysis furnished 1,4-disubstituted [1,2,3]-triazole **6la**, regioselectively in one pot in very good yield (Scheme 2). [1,2,3]-Triazole **6la** was furnished in the same yield via both two and three-component strategies.[15] [1,2,3]-Triazoles have found wide applications in biology, chemistry and materials science,[16] thus new approaches to diverse products are important. We were pleased to find that **5l** also reacted with 1,2-bis-azidomethyl-benzene **4b** in EtOH under $CuSO_4$/Cu-catalysis to furnish the expected di-[1,2,3]-triazole **6lb** in 76% yield with formation of one new carbon–carbon σ bond and four new carbon–nitrogen σ bonds in one pot (Table 3, entry 1).[15] The scope of this dimethylamino-

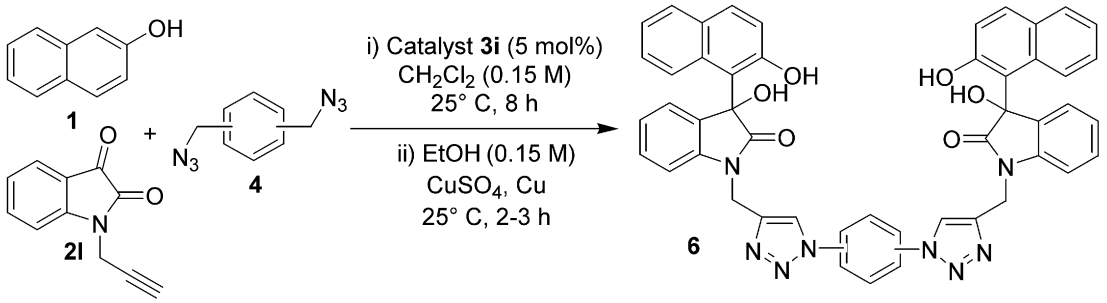


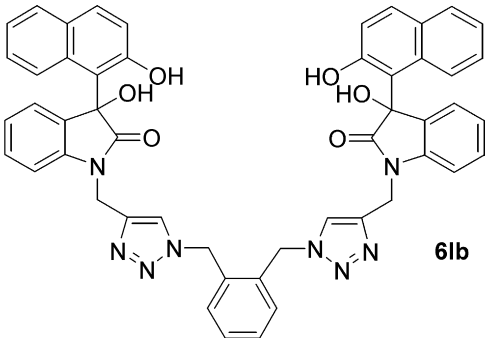
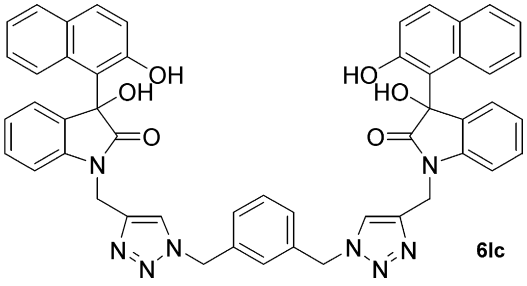
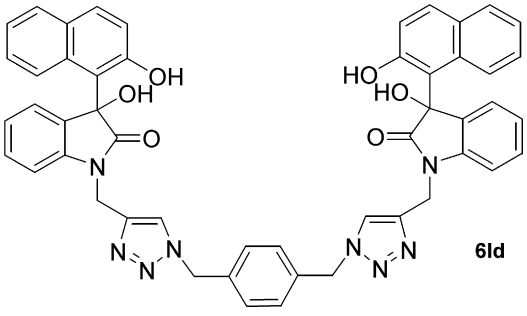
Scheme 2. Organo/Cu^I-catalyzed synthesis of highly substituted 1,2,3-triazole **6la** in one-pot.

ethanol/Cu^I-catalyzed synthesis of compounds of type **6** is revealed by the examples in Table 3.

In summary, we have developed novel dimethylamino-ethanol and dimethylamino-ethanol/Cu^I-catalyzed cascade FCA and FCA/Huisgen cycloaddition reactions through formation of one C–C and four C–N bonds in a single step. This experimentally simple, approach can be used to construct highly substituted 3-aryl-3-hydroxyindolin-2-ones **5** and 1,4-disubstituted [1,2,3]-triazoles **6** in a regioselective fashion with very good

Table 3. Organo/Cu^{I}-catalyzed stereospecific synthesis of polysubstituted triazoles via Friedel–Crafts alkylation/Huisgen cycloaddition reactions in one pot[a]



Entry	Product	Yield[b] (%)
1	 **6lb**	76
2	 **6lc**	80
3	 **6ld**	81

[a] See Section 2.
[b] Yield refers to the column purified product.

yields. Further work is in progress to develop an asymmetric version of this chemistry.

2. Representative experimental procedures

Dimethylamino-ethanol-catalyzed Friedel–Crafts alkylation of 2-naphthols with substituted isatins: In a glass vial equipped with a magnetic stirring bar and containing 0.33 mmol of 2-naphthol **1** and 0.3 mmol of isatin **2a**–**l** was added 2.0 mL of CH_2Cl_2 followed by the catalyst dimethylamino-ethanol **3i** (0.015 mmol) and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1 or 2. Pure Friedel–Crafts alkylation products **5** were obtained by simple filtration of the crude product. High purity products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Dimethylamino-ethanol/Cu^{I}-catalyzed Friedel–Crafts alkylation/Huisgen cycloaddition reactions in one pot: In a glass vial equipped with a magnetic stirring bar and containing 0.33 mmol of 2-naphthol **1** and 0.3 mmol of isatin **2l** was added 2.0 mL of CH_2Cl_2 followed by the catalyst dimethylamino-ethanol **3i** (0.015 mmol) and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. The solvent was removed under vacuum and then EtOH (2.0 mL), $CuSO_4$ (0.33 mmol), Cu wire (5 mg) and benzyl azide **4a** (0.33 mmol) or bis-azidomethyl-benzenes **4b–d** (0.165 mmol) were added and stirring was continued at 25 °C for the time indicated in Table 3. The crude reaction mixture was directly loaded onto a silica gel column without aqueous work-up and pure cascade products **6** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Acknowledgements

We thank DST (New Delhi) for funding this project. We also thank UGC (New Delhi) for recognizing our University of Hyderabad as a 'University with potential for excellence' (UPE) and also recognizing our School of Chemistry as a Center for Advanced Studies in Chemistry and for providing some instrumental facilities. G.B.R. and R.M. thank UGC (New Delhi) and CSIR (New Delhi), respectively, for their research fellowships.

Supplementary data

Experimental procedures and analytical data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.129.

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13. Unfortunately we observed only <10% ee in the cinchona alkaloids, cinchonine **3f** and quinine **3g**, catalyzed FCA reactions of **1** and **2a** in $PhCH_3$ or CH_2Cl_2.
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15. Regiochemistry of the organo-click products **6** were established as 1,4-disubstituted-1,2,3-triazole based on the correlation with previous experiments (see Refs. 5 and 14).
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