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Olefin-Oriented Selective Synthesis of Linear and Branched *N*-Alkylated Heterocycles *via* Hydroamination

Sushmita, Trapti Aggarwal, Kapil Mohan Saini and Akhilesh K. Verma*

Dedication ((optional))

Abstract: An effective base-induced selective approach for the synthesis of linear and branched *N*-alkylated heterocycles *via* hydroamination of olefins has been described. The designed C-N bond formation method was directed through the olefin as with styrenes only linear *N*-alkylated product was obtained and acrylates gave linear as well as branched alkylated heterocycles. This protocol provided the synthesis of exclusive *N*-alkylated product instead of C-3 Michael addition product. The reaction was also compatible with phenyl vinyl sulfone, thus leading to the formation of sulfone substituted heterocycles in good yield. Further, the method was utilizied for the synthesis of medicinally important analogs of CB1 Cannabinoid receptor and Dimebon analouge in short reaction sequence.

The C-N bond-forming reactions contribute as one of the most important, versatile and practical synthetic approach for the development of nitrogen-containing compounds that demonstrate numerous applications in natural products and biologically active drugs.[1-2] Due to the wide applicability of *N*-heterocyles, enormous effort has been devoted for the designing of an economical and mild protocol to furnish *N*-alkylated indoles and carbazoles. Hydroamination of amines with C-C unsaturated bond using expensive metal-catalyst is among the most preferred reaction for the *N*-alkylation of heterocycles because of its high atom economy.[3] Importantly, hydroamination of alkene afforded two possible regioisomeric products, the Markovnikov, and the anti-Markovnikov, which depends on the formation of new C-N bond.[4] Though hydroamination of alkenes typically furnishes the Markovnikov product, however; the participation of the lone pair available on nitrogen in the aromatic system enhance the nucleophilicity at C-3 position of indole. Thus, various reports are available in the literature for C-3 alkylation of indoles[5] however; the challenging task was to execute intermolecular anti-Markovnikov alkylation selectively at nitrogen of indoles instead of C-3 position under mild reaction conditions (Figure 1).

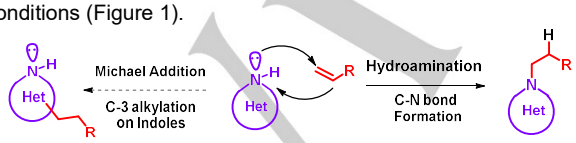

Figure 1. Overview of the Addition of Alkene on *N*-heterocycles

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Tremendous advances has been gained over the past decades with metal-catalyzed alkene hydroamination,[6] however the base-mediated synthesis of linear and branched alkylated heterocycles remains elusive. Interestingly, heterocycles pendant with *N*-alkyl group enhances the biological activity of the molecule.[7] The *N*-alkylated carbazoles core are present in many drugs like AZ-5 (GAT236) CB1 Cannabinoid Receptor (I),[8] latrepirdine or dimebon (II) act as antihistamine drug[9] and Ramatroban (III)[10] used as DP(2) receptor antagonist (Figure 2). The *N*-functionalized carbazoles are in high demand because it increases the solubility of drug in organic solvents.

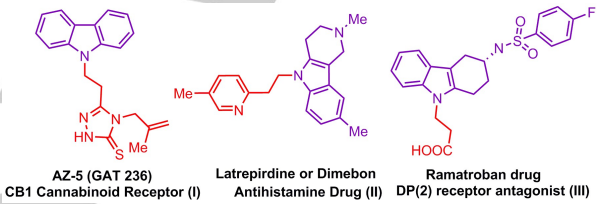
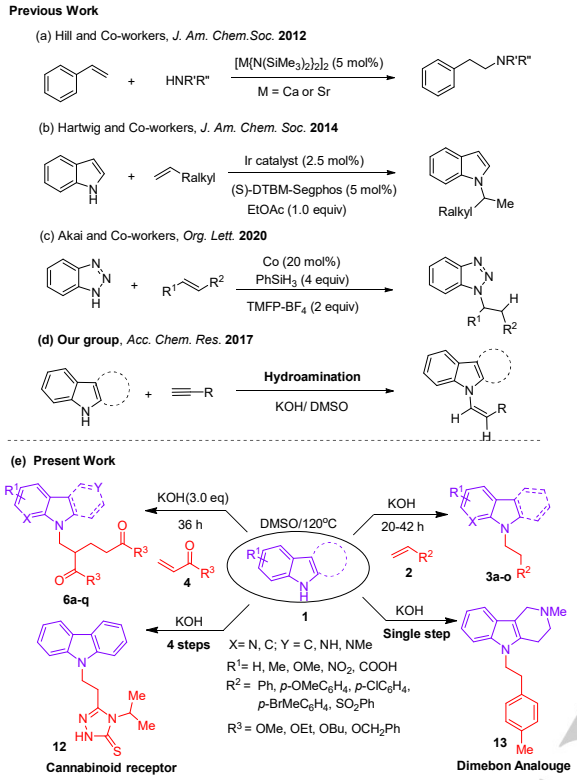


Figure 2. Biologically active carbazoles analogs

In 2012, Hill and co-workers reported the *N*-alkylation of secondary amines with styrenes in the presence of alkaline earth-metal catalysts (Scheme 1a).[11] Later, intermolecular hydroamination of indoles with unactivated olefins in the presence of iridium catalyst was exploited by Hartwig and co-workers to afford the Markonikov addition product (Scheme 1b).[12] Very recently, Akai and co-workers reported the Cobalt-catalyzed alkylation of benzotriazole with alkenes (Scheme 1c).[13] Owing to the high efficacy and versatility of C-N bond formation reaction and our ongoing research on hydroamination with alkynes (Scheme 1d)[14] herein, we wish to explore the base-mediated hydroamination of *N*-heterocycles with olefins including acrylates, olefins, and sulfones (Scheme 1e). To probe the viability of designed protocol, we have synthesized the analogs of CB1 cannabinoid receptors and Dimebon.

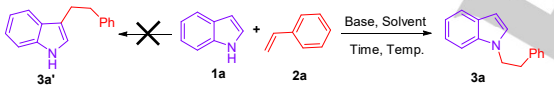
We commenced our investigation on the basis of our previous reports on the hydroamination.[14c] When indole (**1a**) was reacted with phenyl styrene (**2a**) in the presence of 1.0 equiv of KOH in DMSO at 120 °C for 10 h, no progress in the reaction was observed (Table 1, entry 1). Stirring the reaction for a longer time made no significant improvement on the reaction (entry 2). Increase in the amount of base from 2.0 equiv to 3.0 equiv, afforded the 66% yield of *N*-alkylated product **3a** (entries 3-5). Altering the reaction time increases the yield of product **3a** (entry 6-7). Further monitoring the reaction at different temperature afforded the lower yield of product **3a** (entry 8-9). Use of other bases such as NaOH, CsOH provided the product **3a** in lower yield (entries 10-11). Screening of various solvents such as DMF, NMP, DMA and toluene revealed that DMF was the only solvent

suitable for this transformation albeit in lower yield as compared to DMSO (entries 12-15). In the absence of base, no reaction was observed (entry 16).



Scheme 1. Synthesis of *N*-Alkylated Heterocycles

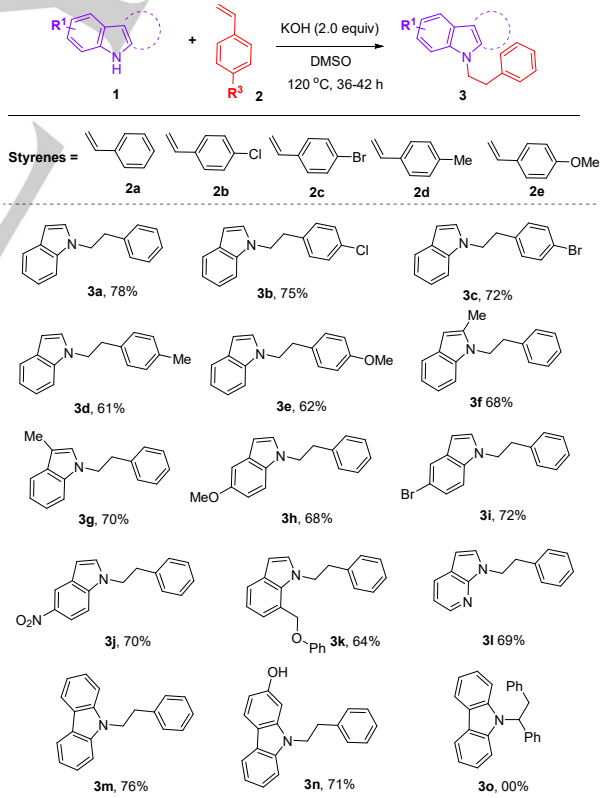
Table 1. *Optimization of reaction conditions.*[a]



entry	solvent	Base (equiv)	temp (°C)	t (h)	yield[b] (%) **3a**
1	DMSO	KOH (1.0)	120	10	0
2	DMSO	KOH (1.0)	120	20	Traces
3	DMSO	KOH (2.0)	120	20	20
4	DMSO	KOH (2.5)	120	20	40
5	DMSO	KOH (3.0)	120	20	66
6	**DMSO**	**KOH (3.0)**	**120**	**36**	**80**
7	DMSO	KOH (3.0)	120	42	81
8	DMSO	KOH (3.0)	140	24	65
9	DMSO	KOH (3.0)	100	36	63
10	DMSO	NaOH (3.0)	120	36	43
11	DMSO	CsOH (3.0)	120	36	37
12	DMF	KOH (3.0)	120	36	55
13	NMP	KOH (3.0)	120	36	NR
14	DMA	KOH (3.0)	120	36	NR
15[c]	Toluene	KOH (3.0)	120	36	NR
16	DMSO	-	120	36	NR

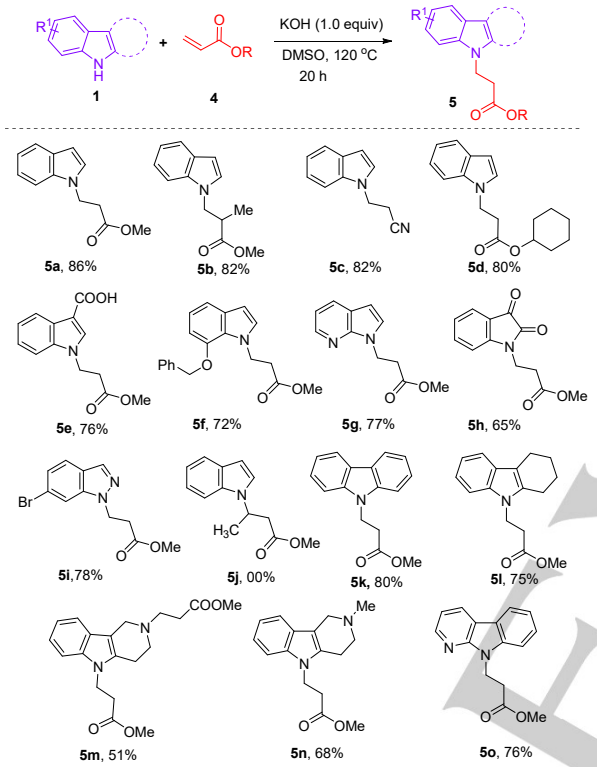
[a] Reactions were performed using 0.50 mmol of **1a**, 0.10 mmol of styrene **2a**, 3.0 equiv of base in 2.0 mL solvent unless otherwise noted. [b] Isolated yield. [c] Without using KOH.

With the optimal reaction condition in hand, a diverse library of *N*-alkylated product **3a–o** was prepared in 60–80% yields. The reaction of indole **1a** with various styrenes **2a–e** afforded the corresponding products **3a–e** in good yields (Scheme 2). A good yield of product **3b** and **3c** were obtained with electron-withdrawing group substituted alkene **2b** and **2c** under the optimal condition. The reaction required 40 h, when styrenes embedded with electron-donating functional group **2d** and **2e** were employed under optimized reaction condition. When methyl substituted indole **1b-1c** were subjected towards the hydroamination reaction, the desired products **3f-g** were obtained in 68% and 70% yield, respectively. The reaction with 5-OMe indole **1d** gave the desired product **3h** in 68% yield. While good yields of product **3i–j** were obtained when bromo and Nitro substituted indole **1e–f** were used as substrate. Interestingly, the reaction proceeds smoothly with 7-(benzyloxy)-1H-indole (**1g**) and afforded the *N*- alkylated product **3k** in 64% yield. The bromo substituted substrate, afforded hydroaminated product over arylation in 78% yield. The optimized reaction condition was compatible with azaindole (**1h**) also to give **3l** in 69% yield. The reaction proceeded smoothly with carbazoles **1i** and hydroxy substituted carbazoles **1j** provided the alkylated products **3m–n** in good yield, devoid of any reaction on free hydroxyl group present in the **1j**. However, no reaction was observed with internal alkene, i.e. *trans*-stilbene **2f**.



Scheme 2. Scope of Styrenes Reaction Conditions: The reactions were performed using *N*-heterocycle **1** (0.5 mmol), 1.0 mmol of Styrenes **2**, 3.0 equiv of KOH in 2.0 mL of DMSO at 120 °C.

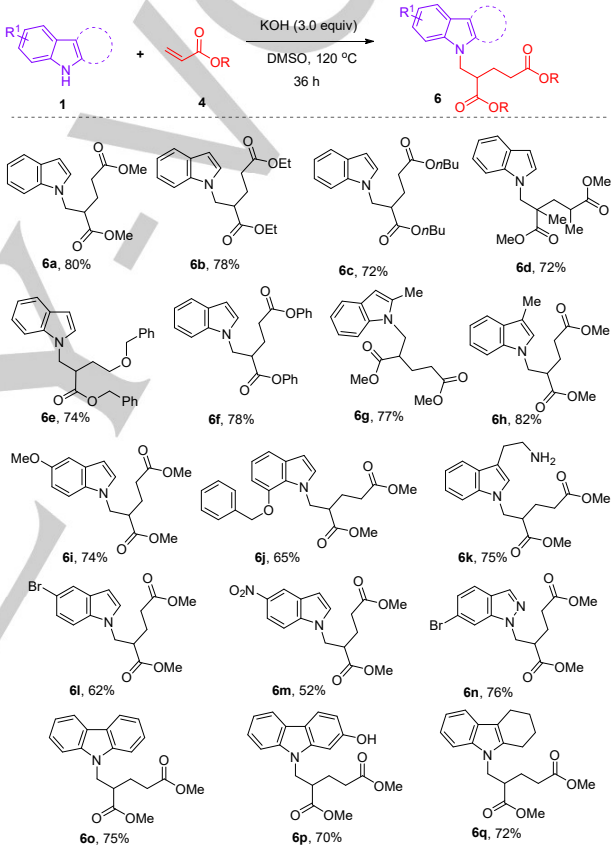
Encouraged from the above results with styrenes, next we intended to explore the hydroamination of *N*-heterocycles with acrylates **4a–e** in super basic medium (Scheme 3). The reaction of indole **1a** with methyl acrylate (**4a**) and methyl methacrylate (**4b**) provided the *N*-alkylated product **5b**–**5b** in 82–86% yield. Acrylonitrile **4c** was well tolerated under the screened reaction condition and afforded the desired product in good yield. The reaction with cyclohexyl acrylate **4d** provided the *N*-alkylated product **5d** in 80% yield. Carboxyl and phenoxyl substituted indole gave *N*-alkylated product in 72-76% yield.



Scheme 3. Scope of Indole/Carbazoles with Acrylates. Reaction Conditions: The reactions were performed using *N*-heterocycle **1** (0.5 mmol), 0.6 mmol of acrylate **4**, 1.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 20 h.

The significant yield of product **5g** was obtained when azaindole **1h** was employed as a substrate. Interestingly, the reaction proceeds smoothly with indoline-2,3-dione (**1l**) and afforded the *N*-alkylated indoline **5h** in 65% yield. Inspired from above results, we next investigated other *N*-heterocycles **1m–q**. When 6-bromo-1H-indazole (**1m**) was used as substrate, the desired *N*-alkylated product **5i** in 78% yield. However, no reaction was observed when indole **1a** was reacted with internal acrylate **4e**. Similarly, unsubstituted carbazole (**1i**) and 1,2,3,4 tetrahydrocarbazole (**1n**) on reaction with methyl acrylate (**2a**) in super basic medium afforded the desired *N*-alkylated product **5k** and **5l** in 80 and 75% yields, respectively. To further extend the scope of substrate, next we utilized biologically active γ-carbolines (**1o–p**).[15] The reaction with substrate having two NH free i.e. γ-carboline **1o**, provided the product **5m** with alkylation on both nitrogens in 51% yield alongwith substrate **1o**. After that, we preceded the reaction with *N*-methyl γ-carbolines **1p** and obtained the selective *N*-alkylated product **5n** in 68% yield. Aza-carbazole **1q** gave the *N*-alkylated product **5o** in good yield.

After the successful synthesis of linear alkylated products **5**, next, we intended to synthesize branched *N*-alkyalted heterocycles **6a-q** *via* hydroamination with successive Michael addition. Using 3.0 equiv of acrylates **2** and KOH, the hydroaminated product **5** *in situ* underwent sequential Michael addition[16] to afford the corresponding branched products **6a– 6q** in good to excellent yields (Scheme 4). The reaction of indole **1a** with methyl acrylate **4a**, ethyl acrylate **4f** and *n*-butyl acrylate **4g** provided the products **6a-c** in 72-80% yield. Methyl methacrylate (**4b**) was also found suitable, giving the desired product **6d** in good yield. Benzyloxy acrylate **4h** and phenyl acrylate **4i** were well tolerated under basic medium to furnish the desired products **6e-f** in 74-78% yields.

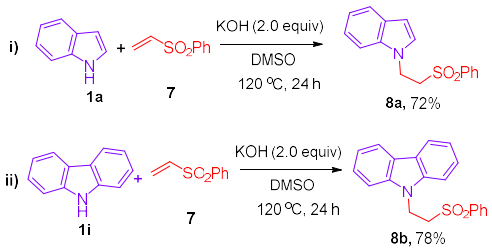


Scheme 4. Synthesis of *N*-pentanedioate substituted heterocycle. Reaction Conditions: The reactions were performed using *N*-heterocycle **1** (0.5 mmol), 1.5 mmol of olefin **4**, 3.0 equiv of KOH in 2.0 mL of DMSO at 120 °C for 36 h.

Substituted indoles with electron-donating groups, such as methyl and methoxy groups, showed good reactivity in the reaction and provide the desired products **6g–6i** in 74–82% yields. Interestingly, 7-(benzyloxy)-1H-indole (**1g**) also found viable for the reaction and furnished the desired product **6j** in 65% yield. The reaction of substrate **1r** having free NH_2 under optimized reaction conditions, chemoselectively provided the product **6k** in 75% yield without affecting free amine group (entry 11). Electron-withdrawing group such as Br and NO_2 substituted indoles **1e-f** afforded the Michael addition products **6l-m** in moderate yields. Bromo-indazole **1m** gave the desired product **6n** in 76% yields. Switching from indole to carbazole scaffold,

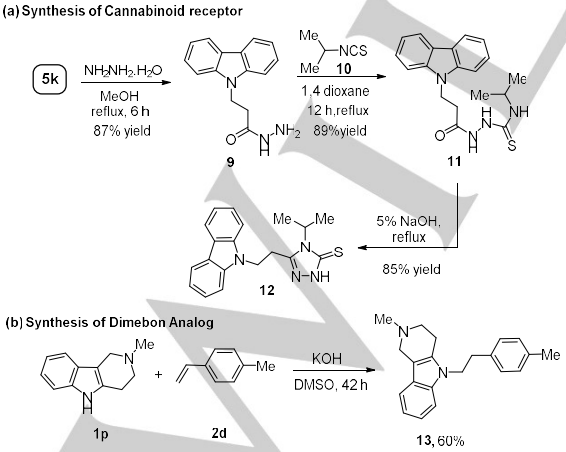
provided the fruitful yield. The reaction of carbazole **1i** with methyl acrylate **4a** afforded the product **6o** in 75% yield. We next extended the substrate scope by employing substituted carbazoles bearing hydroxy at C–2 position **1j**; 70% yield of product **6p** was obtained selectively. Furthermore, tetrahydro carbazole **1n** reacted smoothly with **4a** to provide the product **6q** in good yield.

Inspired from the reaction with styrenes and acrylates, next we planned to utilize electron-deficient vinyl sulfones **7** under the screened reaction condition and obtained the desired product **8a–b** in 72-78% yield (Scheme 5). Sulfones are biologically important synthons which on addition to any scaffold increase its medicinal prospects.[17]



Scheme 5. Reaction of *N*-heterocycle with phenyl vinyl sulfone

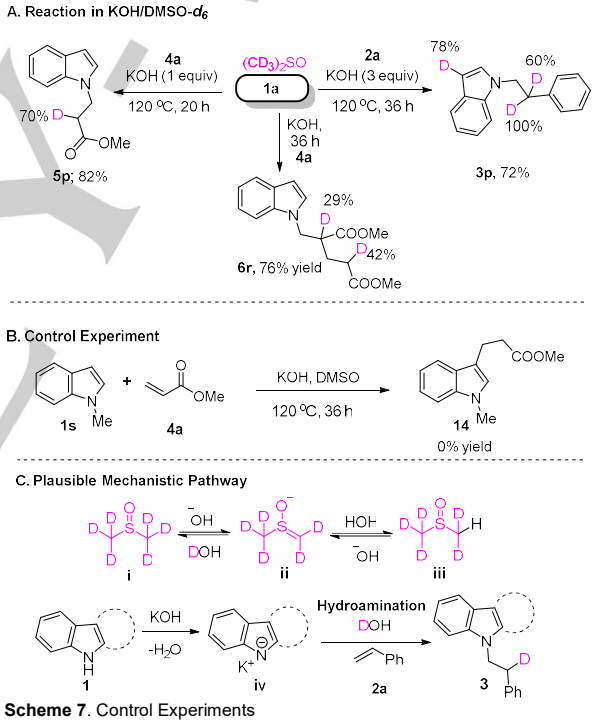
After successful accomplishment with olefins, we elaborated the protocol for the designing of new synthetic route for the medicinally important drug analogs. Firstly, we planned to synthesize the analog of allosteric modulators of CB1 Cannabinoid receptor in short reaction sequence (Scheme 6a). The reaction initiates with condensation reaction between methyl 3-(9*H*-carbazol-9-yl)propanoate (**5k**) and hydrazine hydrate in presence of methanol to give intermediate 9 in 87% yield. Further treating the intermediate **9** with 2-isothiocyanatopropane (**10**), generates thio-semicarbazides **11** in 89% yield which subsequently cyclized in basic medium to form the targeted analog of AZ-5 GAT236 (**12**) (Cannabinoid receptor) in 85% yield. Next, we synthesize Dimebon analog **13** by treating *N*-methyl γ-carboline **1p** as substrate with methyl-substituted styrene **2d** under screened reaction conditions for 42 h. The targeted product **13** was obtained in 60% yield in one-step.



Scheme 6. Synthesis of Allosteric Modulators of CB1 Cannabinoid Receptor and Dimebon analogs

Ivachtchenko group has reported that the alkyl chain present in the products increases its affinity to 5-HT_6 and H_1 receptors.[18]

To support the selective formation of linear and branched hydroaminated product, we conducted deuterium labeling studies (Scheme 7). When we performed the reaction of indole with styrene using DMSO-d_6, product **3p** was obtained in 72% yield with the incorporation of two deuterium molecules at α-to phenyl ring. Then, the formation of deuterated products **5p** in 82% yield after 20 h with 70% deuterium incorporation using DMSO-d_6 supported the initial protonation on the α-carbon adjacent to phenyl/ester group. Using excess of base in DMSO-d_6, provided 76% yield of di-deuterated product **6r** after 36 h. These experiment suggests that the reactions proceed through hydroamination and the incoming protons were provided by the solvent (Scheme 7A). When we performed the reaction with *N*-methyl indole **1s** under basic medium, the expected C-3 alkylated product **14** was not formed (Scheme 7B). Based on the above evidence and literature[14] a plausible mechanism was proposed which shows the exchange of deuterium with hydrogen in presence of KOH generated the DOH which activates the styrene that leads to the formation of hydroaminated product 3 (Scheme 7C).



Scheme 7. Control Experiments

In conclusions, we have reported the selective hydroamination of indoles, carbazoles, aza-carbazoles and γ-carbolines with styrenes, acrylates and sulfones in basic medium. The designed strategy was highly specific and directed through the olefins to furnish linear or branched N-alkylated heterocycles. This protocol provided the *N*-alkylated indoles exclusively with good to excellent yield without C-3 alkylation. We have constructed the diverse library of substituted *N*-pentandioate heterocycles through hydroamination with sequential Michael addition under basic condition. The KOH/DMSO strategy was also compatible with vinyl phenyl sulfones. The developed protocol was then extended for the construction of Dimebon analogue in one-step and AZ-5 CB1

Cannabinoid receptor through short reaction sequence in good yield. The method was well tolerated with variety of functional group which can be easily elaborated through organic functional group transformation. Further, deuterium-labelling experiments supported the mechanistic pathway.

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Keywords: Hydroamination • Indoles• Carbazoles • Styrenes • Acrylates

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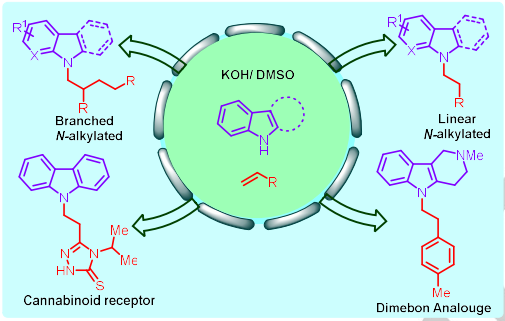
Entry for the Table of Contents

COMMUNICATION

Hydroamination of Olefins



Sushmita, Trapti Aggarwal, Kapil Mohan Saini and Akhilesh K. Verma

Page No. – Page No.

Olefin-Oriented Selective Synthesis of Linear and Branched *N*-Alkylated Heterocycles *via* Hydroamination