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FRIEDEL-CRAFTS REACTION OF INDOLE DERIVATIVES USING THE IMINIUM SALT GENERATED BY THE OXIDATION OF AMINO KETENE SILYL ACETAL

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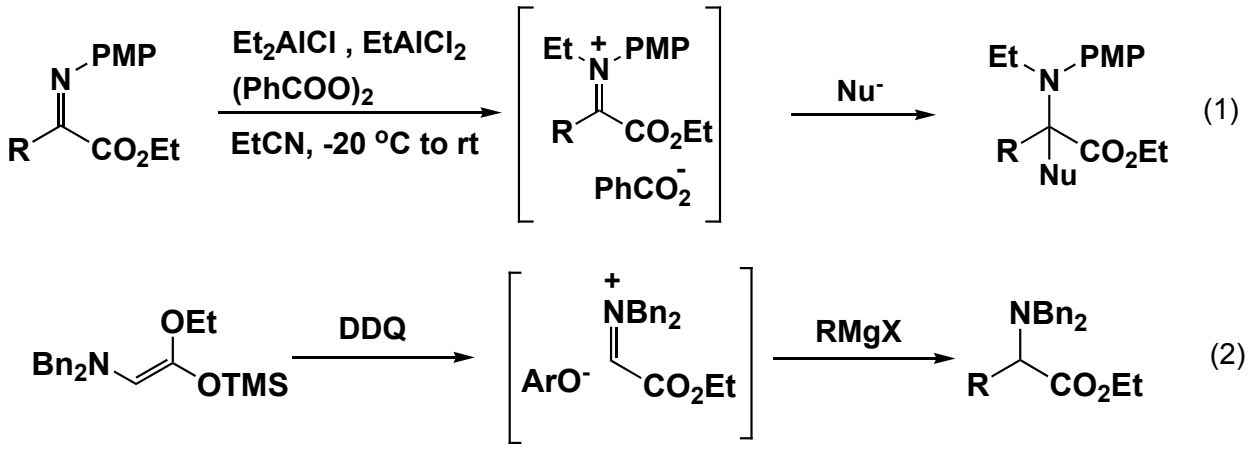
Abstract – Friedel-Crafts reaction of various indole derivatives proceeded with the iminium salt generated by the oxidation of amino ketene silyl acetal to give the addition products in good yields. Further reaction of the introduced glycine moiety of the adducts with the second nucleophiles provided double nucleophilic addition products.

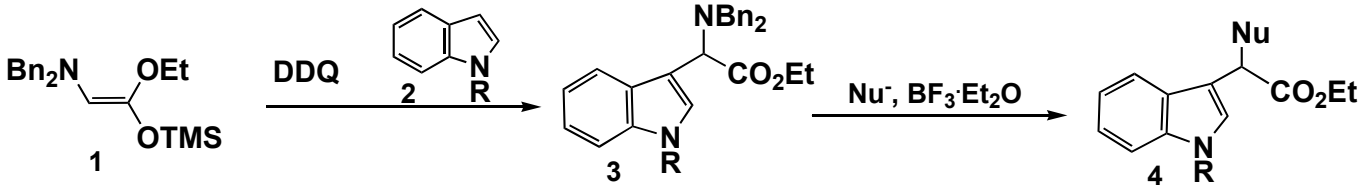
Intriguing reactivity of the iminim salts generated by the oxidation of aluminum enolate derivatives has enabled the use of α-imino esters as acceptors of two nucleophiles (eq 1).[1] Generation of iminium species by the oxidation of the intermediary enolates was extended to the use of amino ketene silyl acetal, readily isolable enolate derivatives as starting materials, and this methodology offers a simple approach to a variety of α-amino esters in a short step (eq 2).[2]



Scheme 1.

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

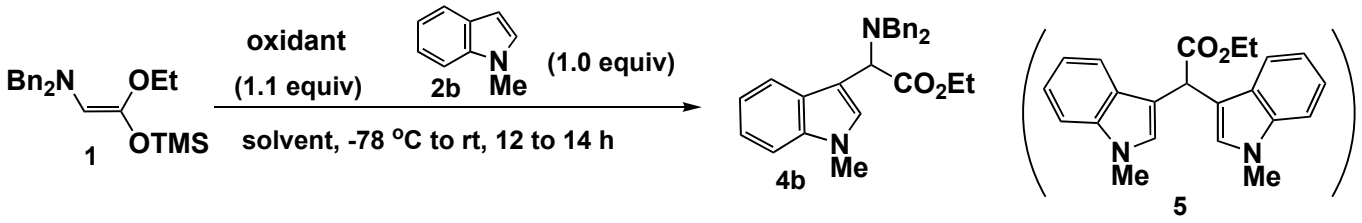
Indole skeletons are often found in many of biologically active compounds such as tryptophan, indomethacin, and dragmacidin derivatives, and several methodologies have been reported to functionalize indoles.[3] When these iminium salts are used as electrophiles, this methodology offers a regio- and chemoselective introduction of a glycine moiety into indoles. Further treatment of this adduct with a second nucleophile in the presence of $BF_3{\cdot}Et_2O$ induces displacement of the dibenzylamino moiety to give a double nucleophilic addition product (**4**).[4]



Scheme 2.

The initial examination was carried out to find optimum Friedel–Crafts reaction conditions using 1-methylindole (**2b**) as nucleophile, and Table 1 summarizes the results.

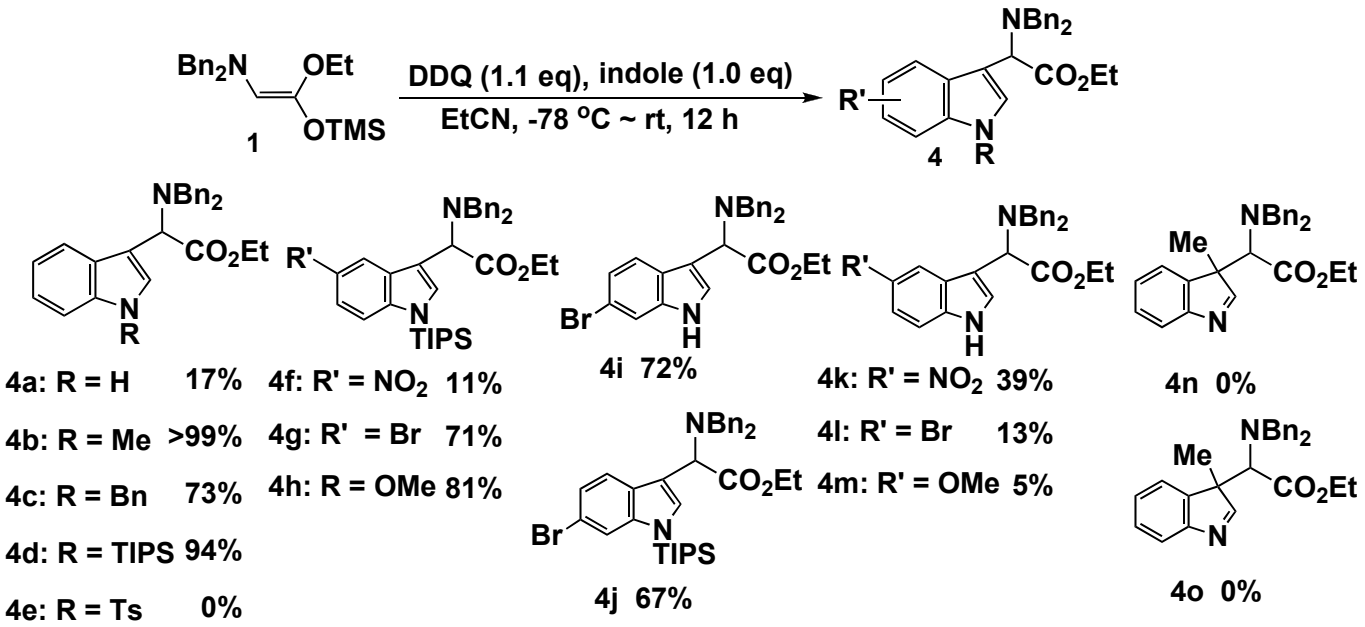
Table 1. Friedel-Crafts Reaction of 1-Methylindole (**2b**) with the Iminium Salt under Various Conditions[a]



Entry	Oxidant	Solvent	Additive (equiv)	**4b** (%)[b]	**5** (%)[b]
1	NCS	EtCN	none	32	0
2	NBS	EtCN	none	22	20
3	NIS	EtCN	none	0	37
4	I_2	EtCN	none	0	42
5	DDQ	EtCN	none	99	0
6	DDQ	CH_2Cl_2	none	96	0
7	DDQ	PhMe	none	88	0
8	DDQ	DMF	none	99	0
9	DDQ	EtCN	$BF_3{\cdot}Et_2O$ (0.5)	67	0
10	DDQ	EtCN	$BF_3{\cdot}Et_2O$ (1.0)	38	12
11	DDQ	EtCN	$BF_3{\cdot}Et_2O$ (2.0)	31	18

[a]Reaction was carried out according to the typical procedure (Ref. 5). [b]Isolated yield.

Regarding the oxidation reagent, use of NCS and NBS gave the adduct (**4b**) in low yields (Entries 1 and 2), whereas NIS and iodine effected the formation of the 1:2 addition product (**5**) (Entries 3 and 4). The best yield of the adduct (**4b**) was obtained, when DDQ was used in EtCN or DMF, where the by-product (**5**) was not formed (Entries 5 and 8). The use of $BF_3{\cdot}Et_2O$ did not noticeably accelerate the addition, but induced the formation of the 1:2 addition product (**5**) (Entries 9 ~ 11). Under the optimum reaction conditions found for the addition of 1-methylindole a variety of indoles were subjected to the Friedel–Crafts reaction, and the representative results are shown in Scheme 2.

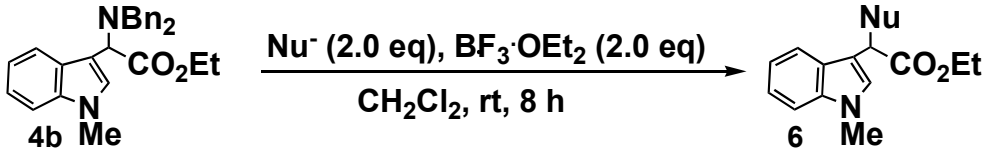


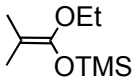
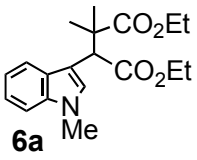
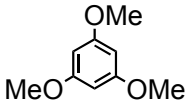
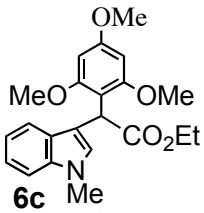
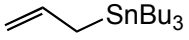
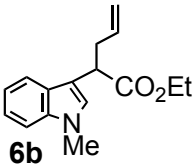
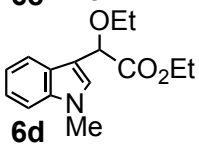
Scheme 2.

Regarding the substituent at the nitrogen of indole, methyl and triisopropylsilyl (TIPS) groups effected the addition efficiently (**4b**, **d**), whereas *p*-toluenesulfonyl (Ts) inhibited the product formation in the absence of a Lewis acid (**4e**). 1-TIPS derivatives having a 5- or 6-substituent were next examined, and the bromo and methoxy derivatives gave the adduct in good yields (**4g**, **h**), while the 5-nitro derivative suppressed the addition reaction (**4f**). Except for the case with 6-bromoindole (**4i**), *N*-unprotected derivatives did not serve as good nucleophiles in the present system, and the adducts were obtained in low yields (**4a**, **k**, **l**, **m**). 3-Methylindoles did not participate in the addition reaction with the present iminium salt (**4n**, **o**).

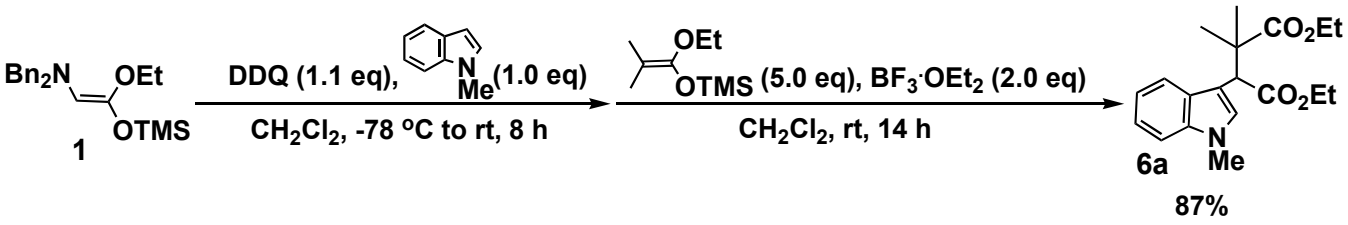
As indicated in Table 1, under certain conditions a 1:2 addition product (**5**) was formed as a by-product, and therefore, we next examined the subsequent nucleophilic displacement of the dibenzylamino moiety of the adduct (**6**). Table 2 summarizes the results.

Table 2. Second Addition to the Adduct (**4b**) in the Presence of $BF_3{\cdot}Et_2O$[a]



Entry	Nucleophile	Product (**6**)	Yield (%)[b]	Entry	Nucleophile	Product (**6**)	Yield (%)[b]
1		 **6a**	78	3		 **6c**	66
2		 **6b**	53	4	EtOH	 **6d**	53[c]

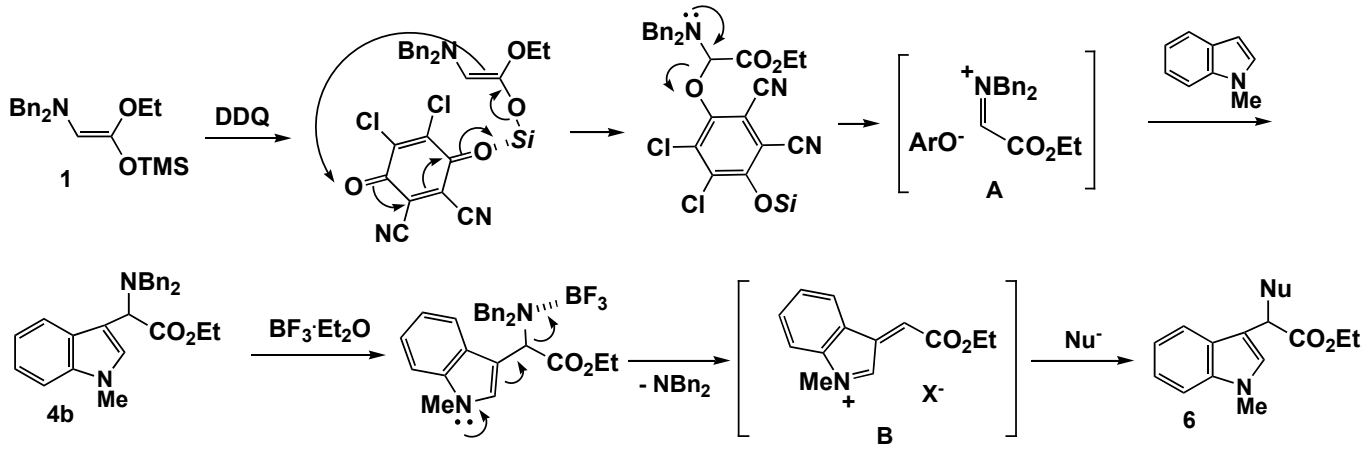
[a] Reaction was carried out according to the typical procedure (Ref. 6). [b] Isolated yield. [c] PPTS was used instead of $BF_3{\cdot}OEt_2$.



After a series of experiments, the best conditions were found for the addition of ketene silyl acetal derived from ethyl isobutyrate, and the adduct (**6a**) was obtained in 78% yield (Entry 1). Under these conditions, allyltrimethylsilane, and 1,3,5-trimethoxybenzene gave the adducts (**6a**, **b**) in moderate yields (Entries 2 and 3). Replacement of the dibenzylamino group with ethanol was effected by pyridinium *p*-toluenesulfonate to give the ethoxy derivative (**6d**) in moderate yield (Entry 4). A one-pot transformation was also carried out using five equivalents of the second nucleophile. In this case the adduct (**6a**) was obtained in 87% yield.

A possible reaction mechanism is depicted in Scheme 3. First, oxidation of the amino ketene silyl acetal (**1**) with DDQ gives the iminium salt (**A**), which in turn is attacked by indole to give the Friedel-Crafts

adduct (**4b**). This adduct is further activated with $BF_3{\cdot}Et_2O$ to give the second iminium salt (**B**). This species would be responsible for the attack of the second nucleophile such as ketene silyl acetal to give the double addition product (**6**).



Scheme 3.

In conclusion, we have found that even in the absence of acid promoters, a facile Friedel-Crafts reaction of indoles proceeded with the iminium salt generated by the oxidation of amino ketene silyl acetal. The Friedel–Crafts adduct was further subjected to the second addition reaction to give the double addition products in good yields. Since a variety of bioactive compounds have indole skeletons and this reaction enables a simple introduction of the glycine moiety into indoles, the present methodology offers a useful addition to the existing functionalization of indoles.

REFERENCES AND NOTES

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5. A typical procedure for the preparation of ethyl 2-dibenzylamino-2-(1-methylindolyl)acetate (**4b**) is as follows: Under an argon atmosphere, 1-ethoxy-2-dibenzylamino-1-trimethylsiloxyethylene (**1**) (0.20 mL, 0.10 mmol, 0.5 M in CH_2Cl_2) and a solution of 1-methylindole (**2b**) (13.1 mg, 0.10 mmol) in DMF were successively added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (25.0 mg, 0.11 mmol) in DMF (1.0 mL) at –78 ºC. The reaction mixture was allowed to warm to ambient temperature with stirring for 14 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the whole mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (EtOAc/*n*-hexane = 1/4) to give ethyl 2-dibenzylamino-2-(1-methylindolyl)acetate (**4b**) (>99%, 41.2 mg) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (t, *J* = 7.3 Hz, 3H), 3.67 (d, *J* = 13.7 Hz, 2H), 3.74 (s, 3H), 3.92 (d, *J* = 13.7 Hz, 2H), 4.21 (dq, *J* = 7.2, 10.7 Hz, 1H), 4.34 (dq, *J* = 7.2, 10.7 Hz, 1H), 4.87 (s, 1H), 7.08-7.12 (m, 3H), 7.20-7.34 (m, 11H), 7.50-7.51 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ : 14.5, 32.8, 54.4, 58.6, 60.3, 109.2, 109.5, 119.3, 121.8, 126.8, 127.6, 128.1, 128.8, 129.1, 137.1, 140.0, 172.4; IR (neat) 3439, 2838, 1727, 1640, 1544, 1452, 1370, 1027, 968, 740, 699, 566, 501 cm^{-1}.
6. A typical procedure for the preparation of diethyl 2,2-dimethyl-3-(1-methylindolyl)succinate (**6a**) is as follows: Under an argon atmosphere, to a solution of ethyl 2-dibenzylamino-2-(1-methylindolyl)acetate (**4b**) (30.5 mg, 0.074 mmol) in CH_2Cl_2 (1.0 mL) were added successively a solution of 1-ethoxy-2-methyl-1-trimethylsiloxypropan-1-ene (28.3 mg, 0.148 mmol) in CH_2Cl_2 (1.5 mL) and $BF_3{\cdot}Et_2O$ (0.148 ml, 0.148 mmol, 1.0 M in CH_2Cl_2) at rt. The reaction mixture was allowed to stand at rt for 5 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the whole mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (developed first with EtOAc/*n*-hexane = 1/4 and then with CH_2Cl_2/*n*-hexane = 1/3) to give diethyl 2,2-dimethyl-3-(1-methylindolyl)succinate (**6a**) (78%, 18.1 mg) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17-1.26 (m, 9H), 1.36 (s, 3H), 3.78 (s, 3H), 4.03-4.19 (m, 4H), 4.42 (s, 1H), 7.09-7.13 (m, 2H), 7.21-7.30 (m, 2H), 7.59-7.61 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ : 14.1, 14.1, 21.2, 25.1, 32.9, 45.7, 48.7, 60.5, 60.7, 107.9, 109.2, 119.2, 119.3, 121.5, 128.4, 129.1, 136.5, 173.3, 177,3; IR (neat) 2948, 1729, 1446, 1216, 1152, 1025, 883, 770, 697, 522, 417 cm^{-1}.