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Iodine-catalyzed allylic alkylation of sulfonamides and carbamates with allylic alcohols at room temperature

Wenhan Wu, Weidong Rao, Ya Qin Er †, Joanna Kejun Loh †, Chai Yun Poh †, Philip Wai Hong Chan *

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

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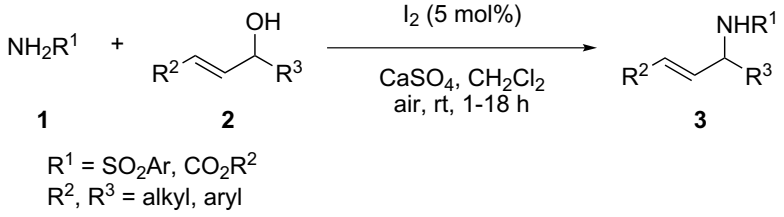
Abstract

A highly efficient iodine-catalyzed allylic alkylation of a wide variety of sulfonamides and carbamates with allylic alcohols is reported herein. The reaction is operationally straightforward and proceeds under very mild conditions at room temperature in good to excellent yields (up to 99%).

Establishing methods to access allylated nitrogen compounds efficiently is currently an active area in organic synthesis due to their importance as intermediates in synthetic strategies to bioactive natural products and pharmaceutically interesting compounds.[1] Among the myriad of works devoted to this reaction, those directed towards new methods that make use of inexpensive and readily available electrophiles, mild reaction conditions, simple manipulation, atom-economy, and environmentally friendly catalysts have become very topical.[2–8] Indeed, a recent notable example was the use of allylic alcohols as the allylating reagent in the presence of a metal catalyst (usually Pd) which furnished H_2O as the only side product.[4] The respective groups of Shibasaki[5] and Liu[6] showed that a similar approach could be employed for the allylic alkylation of less nucleophilic sulfonamide and carbamate substrates at room temperature through the use of the Lewis acids $Bi(OTf)_3$ and $AuCl_3$ as catalysts. Despite these advances, it remains a challenge to develop a metal catalyst-free and operationally simple version of this useful carbon–nitrogen bond forming reaction that can be accomplished under mild conditions. In this context, we envisioned that



Scheme 1.

* Corresponding author. Tel.: +65 6316 8760; fax: +65 6791 1961.
E-mail address: waihong@ntu.edu.sg (P. W. H. Chan).
† Equal contributions to this work.

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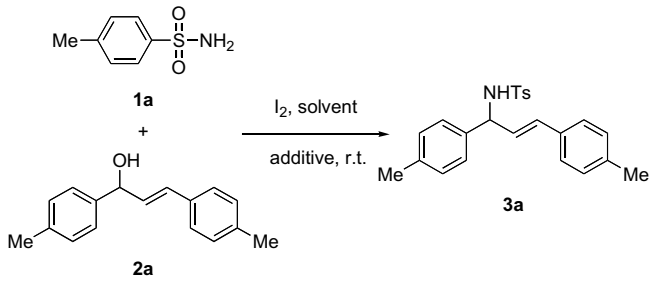
molecular iodine would hold promise as a catalyst for amide allylation with allylic alcohols. An inexpensive, commercially available reagent that has a high tolerance to air and moisture, we and others have recently shown molecular iodine to be versatile in mediating a wide variety of organic transformations in excellent yields and with high selectivity.[7] Recently, we reported that molecular iodine could mediate the allylic alkylation of 1,3-dicarbonyl compounds in good to excellent yields.[8] In view of this work, we were keen to examine whether the same catalytic protocol could be extended to the allylic alkylation of sulfonamides and carbamates with allylic alcohols. As part of an ongoing program on carbon-nitrogen bond formations in our group,[9] we report herein the allylic alkylation of a wide variety of sulfonamides and carbamates with allylic alcohols catalyzed by molecular iodine that proceeded in good to excellent yields (up to 99%), at room temperature, and without the need for inert and moisture-free reaction conditions (Scheme 1).

We found that treating a solution of *p*-toluenesulfonylamide **1a** (1 equiv), (*E*)-1,3-di-*p*-tolylprop-2-en-1-ol **2a** (1.5 equiv) and $CaSO_4$ (50 mg) in CH_2Cl_2 with 5 mol % of iodine as catalyst in an open round-bottom flask at room temperature for 2.5 h gave the best result, furnishing (*E*)-1,3-di-*p*-tolyl-*N*-tosylprop-2-en-1-amine **3a** in 85% yield (Table 1, entry 1).[10] The retention of trans-stereochemistry in the allylated product was confirmed by ^1H NMR analysis and X-ray crystal structure determination, as shown in Figure 1a.[11] On the other hand, slightly lower product yields of 67–68% were observed when the reaction was carried out in the absence of a drying reagent or conversely in an oven-dried closed reaction vessel under an argon atmosphere, suggesting that a trace amount of water promotes the allylation reaction (entries 2 and 5). Similarly, lower product yields of 65–70% were obtained on changing the drying reagent to $MgSO_4$ or 4 Å MS, and with C_6H_6 as the solvent (entries 3, 4 and 12). In contrast, analogous reactions conducted without a drying reagent in other solvents were less effective and lower product yields of 9–50% were obtained for reactions in $CHCl_3$, 1,4-dioxane, MeCN, THF or PhMe (entries 7–11). As anticipated, no reaction was observed in the absence of the iodine catalyst and both starting materials were recovered in quantitative yields (entry 6).

To define the scope of the iodine-catalyzed reactions, we applied this process to a series of substituted sulfonamides and carbamates **1a–g** and allylic alcohols **2a–i**. As shown in entries 1–8 in Table 2, allylation of a variety of *para*-substituted arylsulfonamides with allylic alcohols bearing electron-withdrawing and electron-donating groups proceeded in good to excellent yields comparable to those obtained in the analogous metal-catalyzed reactions.[4–6]

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	Additive	Yield[b] (%)
1	CH_2Cl_2	$CaSO_4$	85
2[c]	CH_2Cl_2	$CaSO_4$	67
3	CH_2Cl_2	$MgSO_4$	70
4	CH_2Cl_2	4 Å MS	70
5	CH_2Cl_2	—	68
6[d]	CH_2Cl_2	—	—[e]
7	$CHCl_3$	—	38
8	1,4-Dioxane	—	45
9	MeCN	—	50
10	THF	—	37
11	PhMe	—	9
12	C_6H_6	—	65

[a] All reactions were performed at room temperature for 3 h with an I_2:**1a**:**2a** ratio = 1:20:30.
[b] Isolated yield.
[c] Reaction conducted in a dry closed reaction vessel under an Ar atmosphere.
[d] Reaction conducted in the absence of I_2 catalyst.
[e] No reaction after 5 h based on TLC analysis.

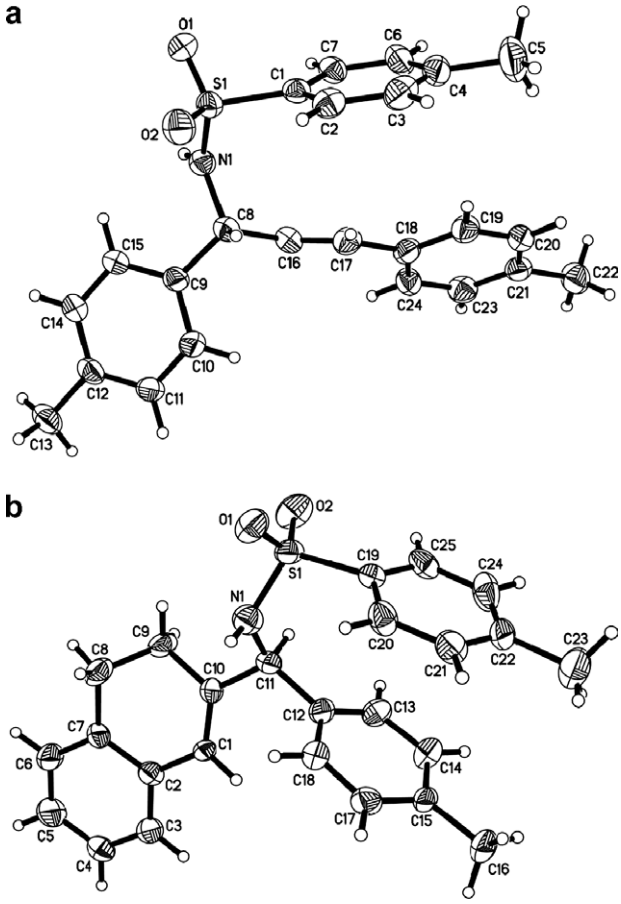
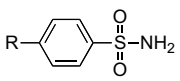
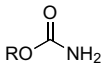


Fig. 1. ORTEP drawings of (a) **3a** and (b) **3v** with thermal ellipsoids at 50% probability levels.[11]

Table 2
Iodine-catalyzed allylation of sulfonamides and carbamates **1a**–**g** with allylic alcohols **2a**–**i**[a]

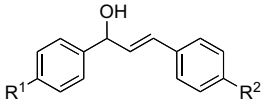


1b, R = OMe
1c, R = F

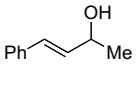


1d, R = Bn
1e, R = ^{i}Pr
1f, R = ^{t}Bu

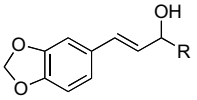
1g



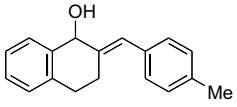
2b, $R^1 = R^2 = H$
2c, $R^1 = R^2 = Br$
2d, $R^1 = Cl$, $R^2 = Me$
2e, $R^1 = Br$, $R^2 = OEt$



2f



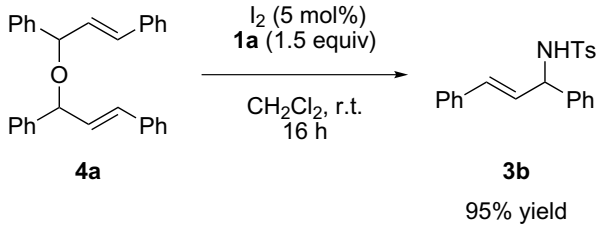
2g, R = Me
2h, R = Ph



2i

Entry	Substrates	Product	Yield[b] (%)
1	**1a** + **2b**	**3b**, $R^1 = R^2 = H$, $R^3 = Me$	85
2	**1a** + **2c**	**3c**, $R^1 = R^2 = Br$, $R^3 = Me$	65
3	**1a** + **2d**	**3d′**, $R^1 = Cl$, $R^2 = R^3 = Me$ **3d″**, $R^1 = R^3 = Me$, $R^2 = Cl$	89[c]
4	**1a** + **2e**	**3e′**, $R^1 = Br$, $R^2 = OEt$, $R^3 = Me$ **3e″**, $R^1 = OEt$, $R^2 = Br$, $R^3 = Me$	61[d]
5	**1b** + **2a**	**3f**, $R^1 = R^2 = Me$, $R^3 = OMe$	86
6	**1b** + **2b**	**3g**, $R^1 = R^2 = H$, $R^3 = OMe$	89
7	**1c** + **2a**	**3h**, $R^1 = R^2 = Me$, $R^3 = F$	51
8	**1c** + **2b**	**3i**, $R^1 = R^2 = H$, $R^3 = F$	72
9	**1d** + **2b**	**3j**, $R^1 = R^2 = H$, $R^3 = Bn$	92
10	**1e** + **2b**	**3k**, $R^1 = R^2 = H$, $R^3 = {}^{i}Pr$	96
11	**1f** + **2b**	**3l**, $R^1 = R^2 = H$, $R^3 = {}^{t}Bu$	93
12	**1f** + **2a**	**3m**, $R^1 = R^2 = Me$, $R^3 = {}^{t}Bu$	93
13	**1f** + **2c**	**3n**, $R^1 = R^2 = Br$, $R^3 = {}^{t}Bu$	66
14	**1f** + **2d**	**3o′**, $R^1 = Cl$, $R^2 = Me$, $R^3 = {}^{t}Bu$ **3o″**, $R^1 = Me$, $R^2 = Cl$, $R^3 = {}^{t}Bu$	94[e]
15	**1g** + **2b**	**3p**	94
16	**1a** + **2f**	**3q**	64
17	**1a** + **2g**	**3r**, R = Ts	62
18	**1f** + **2g**	**3s**, R = Boc	66
19	**1a** + **2h**	**3t**, R = Ts	74[f]
20	**1f** + **2h**	**3u**, R = Boc	92[f]
21	**1a** + **2i**	**3v**, R = Ts	81
22	**1f** + **2i**	**3w**, R = Boc	73

[a] All reactions were performed at room temperature for 3 h with an I_2:**1**:**2** ratio = 1:20:30 in a solution of CH_2Cl_2.
[b] Isolated yield.
[c] Isolated as an inseparable mixture of regioisomers in the ratio = 2.6:1.
[d] Isolated as an inseparable mixture of regioisomers in the ratio = 2:1.
[e] Isolated as an inseparable mixture of regioisomers in the ratio = 2.8:1.
[f] Isolated as an inseparable mixture of regioisomers in the ratio = 1.7:1.



Scheme 2.

The present procedure was also shown to work well for the allylation of a variety of alkyl substituted carbamates, giving the corresponding allylated adducts in good to excellent yields (entries 9–14). Notably, this included the allylation of cyclic carbamate **1g** with **2b**, which gave **3p** in excellent yield (entry 15). In cases where it was envisaged that reactions with allylic alcohols containing two very different substituents such as an aryl and alkyl group as in **2f–g** and **2i** would lead to a mixture of regioisomeric products, the exclusive formation of only one product indicates that the present procedure is regioselective (entries 16–18 and 21 and 22). This was further confirmed by X-ray structure analysis of **3v**, as shown in Figure 1b.[11] The allylations of **1a** and **1f** with either **2d**, **2e** or **2h**, which contain two slightly different *para*-substituted aryl groups, were the only examples to give poor regioselectivity. In these reactions the corresponding allylated adducts **3d**, **3e**, **3o**, **3t** and **3u** were furnished as a mixture of inseparable regioisomers in ratios ranging from 1.7 to 2.8:1 (entries 3, 4, 14 and 19, 20). Consistent with our earlier findings for the analogous allylation of 1,3-dicarbonyl compounds,[8] in all the above reactions competitive formation of an ether side-product resulting from dimerization of **2** (see later and Scheme 2) was observed by TLC analysis.

Although currently unclear, we tentatively propose that the mechanism of the present procedure proceeds in a manner similar to that for the allylation of 1,3-dicarbonyl compounds with allylic alcohols.[8] This involves the formation of an allylic carbocation species from the reaction of the allylic alcohol **2** with HI generated in situ. The regioselectivities obtained in these reactions could be due to subsequent attack at the sterically less hindered carbon of this presumed allylic carbocation intermediate by **1** or another molecule of **2** to produce the reactive dimer **4** of the type shown in Scheme 2, which reacts further in the presence of **1** to give the allylated product **3**. To support the possible involvement of such intermediates, we undertook the following experiments. The dimer **4a**, obtained as a mixture of diastereomers from the reaction of **2b** with 5 mol % of iodine following the literature procedure,[8] could be converted to **3b** in 95% yield on treatment with 1.5 equiv of **1a** and 5 mol % of iodine catalyst in CH_2Cl_2 for 16 h at room temperature (Scheme 2). In addition, **3b** was furnished in a comparable yield of 90% for the analogous reaction of **1a** with **2b** under the same conditions as those described in Table 2, entry 1 but with NaI (5 mol %) and trifluoroacetic acid (5 mol %) in place of iodine as catalyst.

In summary, we have demonstrated a practical and operationally simple method for the allylation of sulfonamides and carbamates with allylic alcohols under atmospheric conditions at room temperature that proceeded in good to excellent yields. The present protocol is applicable to a variety of sulfonamides, carbamates and allylic alcohols containing electron-withdrawing, electron-donating and sterically demanding substrate combinations. Efforts are currently underway to examine the scope and mechanism of this carbon–nitrogen bond formation strategy.

Acknowledgements

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10. *Typical experimental procedure*: To a CH_2Cl_2 (1 mL) solution of **1** (0.3 mmol, 1 equiv), **2** (0.45 mmol, 1.5 equiv) and $CaSO_4$ (50 mg) in a round-bottom flask open to air at room temperature was added molecular iodine (15 μmol, 5 mol %). The reaction was stirred for 3 h and then quenched with aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated, and purified by flash silica gel column chromatography (*n*-hexane/EtOAc as eluent) to give **3**.
11. CCDC 673120 and 673121 (**3a** and **3v**, respectively) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.