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Efficient synthesis of *o*-alkynyl-*N*-pivaloylanilines from *o*-acyl-*N*-pivaloylanilines and lithium trimethylsilyldiazomethane

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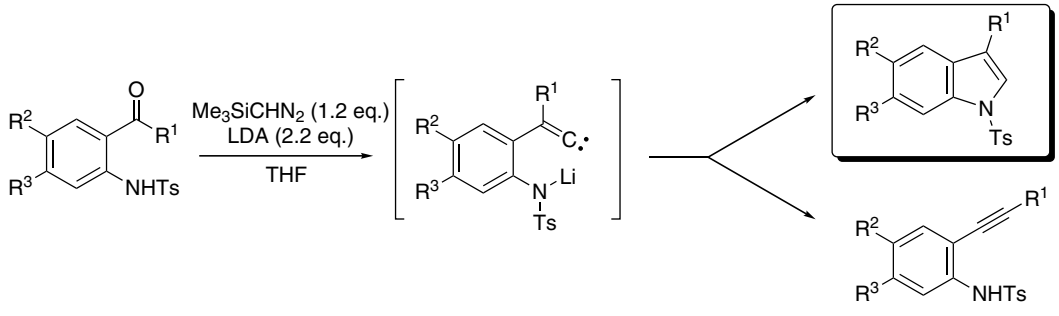
Abstract—Reaction of *o*-acyl-*N*-pivaloylanilines with lithium trimethylsilyldiazomethane efficiently gave the corresponding *o*-alkynyl-*N*-pivaloylanilines via alkylidenecarbene intermediates.

o-Alkynylanilines serve as an important precursor for the construction of heterocyclic structures, for example, indole,[1,2] quinoline[3] and cinnoline skeletons.[4] Although there are a few synthetic methods of *o*-alkynylanilines,[5,6] the practical method would be limited to Sonogashira coupling reaction between *o*-iodoanilines and terminal alkynes.[5] Therefore, development of additional synthetic approaches to *o*-alkynylanilines would be still required in the field of heterocyclic chemistry.

Recently, we have revealed that the lithium salt of trimethylsilyldiazomethane (TMSC(Li)N_2), a quite useful reagent for generating alkylidenecarbenes from carbonyl compounds,[7,8] smoothly reacts with *o*-acyl-*N*-tosylanilines to selectively give 3-substituted *N*-tosylindoles (the intramolecular N–Li insertion products) via alkylidenecarbene intermediates (Scheme 1).[9] In some cases, small amounts of *o*-alkynyl-*N*-tosylanilins (the rearrangement products) were formed as by-products. On the other hand, interestingly, under similar conditions, when *o*-acetylacetanilide was used as a substrate, the major product was the rearrangement product, *o*-(1-propynyl)acetanilide (46%), though the desired indole (21%) was also obtained.[9] These results indicate that the reaction pathway was significantly affected by a substituent on an amino group. Therefore, we reinvestigated the reaction of *N*-acyl-*o*-acylanilines with TMSC(Li)N_2 in order to yield *N*-acyl-*o*-alkynylanilines selectively. This letter describes our results.

First, screening of *N*-substituents was carried out as shown in Table 1.[10,11] As standard reaction conditions, we employed $TMSCHN_2$ (1.2 equiv) and *n*-BuLi (2.2 equiv), in which the latter was used as a base for the preparation of TMSC(Li)N_2 and for deprotonation of the N–H moiety of a substrate. As expected, reaction



Scheme 1. Reaction of *o*-alkynyl-*N*-tosylanilines with TMSC(Li)N_2.

Keywords: *o*-Acylanilines; Alkylidenecarbenes; *o*-Alkynylanilines; Lithium trimethylsilyldiazomethane; Trimethylsilyldiazomethane.
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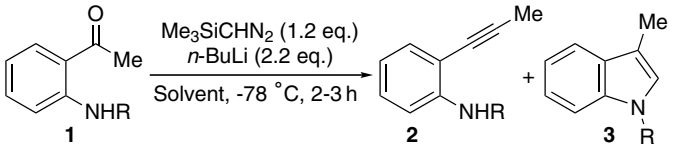
Table 1. Reaction of *o*-acetyl-*N*-acylanilines



Entry	R	Solvent	Yield (%)[b]
1	Bz (**a**)	THF	62 (**2a**)+4 (**3a**)+3[c]
2	*p*-MeOPhCO (**b**)	THF	56 (**2b**)
3[c]	*o*-MePhCO (**c**)	THF	38 (**2c**)+9[c]
4	Piv (**d**)	THF	74 (**2d**)+8 (**3d**)
5[a]	Piv (**d**)	THF	69 (**2d**)+10 (**3d**)
6	Piv (**d**)	Et_2O	61 (**2d**)+16 (**3d**)

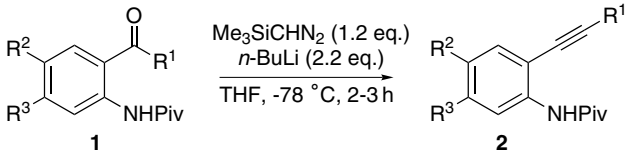
[a] *n*-BuLi (1.2 equiv) was used.
[b] Isolated yield.
[c] Yield of 3-methylindole.

of TMSC(Li)N_2 with **1a–d** bearing a benzoyl, *p*-methoxybenzoyl, *o*-methylbezoyl or pivaroyl group as *N*-substituents in THF smoothly proceeded and the desired *o*-(1-propynyl)anilides **2a–d** were preferentially obtained in all cases (entries 1–4). Among them, **1d** bearing a bulky pivaroyl group gave the best result (entry 4). Interestingly, in this reaction, the use of a reduced amount of *n*-BuLi also afforded **2d** in good yield (entry 5). This result indicates that there might be equilibrium between TMSC(Li)N_2 and the N–Li form of the amide. Very recently, it has been reported that the use of Et_2O, having lower E_T-value[12] than that of THF, as solvent increases the ratio of the alkyne to the indole in the reaction of TMSC(Li)N_2 with *o*-aminobenzophenone.[13] However, reaction with **1d** in Et_2O led to a less effective result (entry 6).

Under the most efficient reaction conditions as shown in entry 4 of Table 1, generality of the reaction was investigated (Table 2).[11] Reaction of TMSC(Li)N_2 with **1e** and **1f** bearing alkanoyl groups, such as pentanoyl and isobutyryl groups, as an acyl moiety, successfully afforded the desired *o*-alkynyl-*N*-pivaloylanilines **2e** and **2f** as the sole isolable product in 82% and 76% yields, respectively (entries 1 and 2). Similarly, the formyl derivative **1g** gave **2g** in 50% yield (entry 3). Substrates **1h–j** bearing aroyl groups also underwent the reaction with TMSC(Li)N_2 giving the corresponding **2h–j** (entries 4–6). Especially, 2-furyl derivative **1j** gave the high yield (84%). Although reaction of the *p*-iodoanilide **1l** also proceeded, the product was the deiodinated alkynylanilide **2d**, not the *p*-iodo derivative **2l**, resulting from iodine–lithium exchange reaction (entry 8). However, the use of the reduced amount of *n*-BuLi described above led to a significant improvement of the reaction and the desired **2l** was obtained in 51% yield without formation of **2d** (entry 9). This reaction will be valuable since the synthesis of (*o*-alkynyl)iodoanilines by Sonogashira reaction of diiodoanilines with terminal alkynes is usually difficult. Other substrates **1m–o** also gave the corresponding alkynes **2m–o** in 63–82% yields (entries 10–12).

In conclusion, we have found that *o*-acyl-*N*-pivaloylanilines reacted with TMSC(Li)N_2 to selectively give

Table 2. Reaction of *o*-acyl-*N*-pivaloylanilines **1** with TMSC(Li)N_2[a]



Entry	Substrate	R^1	R^2	R^3	Yield (%)
1	**1e**	*n*-Bu	H	H	82 (**2e**)
2	**1f**	*i*-Pr	H	H	76 (**2f**)
3	**1g**	H	H	H	50 (**2g**)
4	**1h**	Ph	H	H	50 (**2h**)
5	**1i**	2-Pyridyl	H	H	58 (**2i**)[b]
6	**1j**	2-Furyl	H	H	84 (**2j**)
7	**1k**	Me	–OCH_2O–		63 (**2k**)[b]
8	**1l**	Me	I	H	56 (**2d**)[c]
9	**1l**	Me	I	H	51 (**2l**)[d]
10	**1m**	H	Me	H	64 (**2m**)
11	**1n**	*i*-Pr	Me	H	82 (**2n**)
12	**1o**	*i*-Pr	–CH=CH–CH=CH–		63 (**2o**)

[a] In all cases, 3-substituted indole was not obtained.
[b] Substrates **1i** and **1k** were recovered in 6% and 7% yields, respectively.
[c] The desired iodo derivative **2l** was not obtained.
[d] *n*-BuLi (1.2 equiv) was used.

o-alkynyl-*N*-pivaloylanilines. This method would provide a new and efficient synthetic access to *o*-alkynylanilines, which are useful precursors for construction of heterocyclic skeletons. Moreover, this result and our previous report[9] are noteworthy in demonstrating that the difference between tosyl and pivaloyl groups as *N*-substituents of *o*-acylanilines in reaction with TMSC(Li)N_2 would bring about divergent reaction of their alkylidenecarbene intermediates, namely, N–Li insertion reaction and rearrangement reaction.

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10. Typical procedure (entry 4 in Table 1). To a stirred solution of $TMSCHN_2$ (1.7 M in hexane, 0.37 ml, 0.6 mmol) in THF (3 ml), *n*-BuLi (1.6 M in hexane, 0.69 ml, 1.1 mmol) was added dropwise at −78 °C under argon atmosphere and the mixture was stirred at −78 °C for 20 min. A solution of **1d** (108 mg, 0.5 mmol) in THF (3 ml) was then added to the above mixture at −78 °C. The whole mixture was stirred at −78 °C for 2 h. After addition of water, the mixture was extracted with AcOEt. The organic extracts were washed with water and brine, dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane–AcOEt (20:1) as eluent to give *N*-pivaloyl-*o*-(1-propynyl)aniline **2d** (80 mg, 74%) and 3-methyl-*N*-pivaloylindole **3d** (8.6 mg, 8%).
11. Selected data for **2a**–**o**. Compound **2a**, ^{1}H NMR ($CDCl_3$) δ: 2.18 (3H, s), 7.05 (1H, dt, $J = 1.0$ and 7.5 Hz), 7.34 (1H, t, $J = 8.0$ Hz), 7.40 (1H, t, $J = 8.0$ Hz), 7.48–7.60 (3H, m), 7.92 (2H, dd, $J = 1.0$ and 8.0 Hz), 8.57 (1H, d, $J = 8.0$ Hz), 8.84 (1H, br s). Compound **2b**, ^{1}H NMR ($CDCl_3$) δ: 2.19 (3H, s), 3.88 (3H, s), 6.98–7.06 (3H, m), 7.31–7.41 (2H, m), 7.88 (2H, d, $J = 8.5$ Hz), 8.55 (1H, d, $J = 8.0$ Hz), 8.77 (1H, br s). Compound **2c**, ^{1}H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.57 (3H, s), 7.05 (1H, t, $J = 7.5$ Hz), 7.28–7.41 (5H, m), 7.57 (1H, d, $J = 8.0$ Hz), 8.36 (1H, br s), 8.55 (1H, d, $J = 8.0$ Hz). Compound **2d**, ^{1}H NMR ($CDCl_3$) δ: 1.35 (9H, s), 2.16 (3H, s), 6.99 (1H, t, $J = 7.5$ Hz), 7.26–7.36 (2H, m), 8.40–8.43 (2H, m). Compound **2e**, ^{1}H NMR ($CDCl_3$) δ: 0.96 (3H, t, $J = 7.0$ Hz), 1.35 (9H, s), 1.46–1.54 (2H, m), 1.62 (2H, q, $J = 7.0$ Hz), 2.51 (2H, t, $J = 7.0$ Hz), 6.99 (1H, t, $J = 8.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz), 7.35 (1H, d, $J = 8.0$ Hz), 8.38–8.43 (2H, m). Compound **2f**, ^{1}H NMR ($CDCl_3$) δ: 1.50 (6H, d, $J = 7.0$ Hz), 1.53 (9H, s), 3.07 (1H, sept, $J = 7.0$ Hz), 7.17 (1H, t, $J = 7.5$ Hz), 7.42–7.50 (1H, m), 7.54 (1H, d, $J = 7.5$ Hz), 8.57 (1H, br s), 8.61 (1H, d, $J = 8.0$ Hz). Compound **2g**, ^{1}H NMR ($CDCl_3$) δ: 1.34 (9H, s), 3.54 (1H, s), 7.03 (1H, t, $J = 8.0$ Hz), 7.36 (1H, t, $J = 8.0$ Hz), 7.45 (1H, d, $J = 8.0$ Hz), 8.35 (1H, br s), 8.45 (1H, d, $J = 8.0$ Hz). Compound **2h**, ^{1}H NMR ($CDCl_3$) δ: 1.36 (9H, s), 7.06 (1H, t, $J = 8.0$ Hz), 7.34 (1H, d, $J = 8.0$ Hz), 7.38–7.40 (3H, m), 7.49–7.55 (3H, m), 8.42 (1H, br s), 8.48 (1H, d, $J = 8.0$ Hz). Compound **2i**, ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 7.06 (1H, t, $J = 7.0$ Hz), 7.20–7.29 (1H, m), 7.38 (1H, t, $J = 8.0$ Hz), 7.48–7.55 (2H, m), 7.71 (1H, t, $J = 8.0$ Hz), 8.47–8.50 (2H, m), 8.64 (1H, br s). Compound **2j**, ^{1}H NMR ($CDCl_3$) δ: 1.35 (9H, s), 6.44 (1H, dd, $J = 2.0$ and 3.5 Hz), 6.68 (1H, d, $J = 3.5$ Hz), 7.03 (1H, t, $J = 8.0$ Hz), 7.34 (1H, t, $J = 8.0$ Hz), 7.44–7.46 (2H, m), 8.34 (1H, br s), 8.45 (1H, d, $J = 8.0$ Hz). Compound **2k**, ^{1}H NMR ($CDCl_3$) δ: 1.25 (9H, s), 2.05 (3H, s), 5.85 (2H, s), 6.69 (1H, s), 7.94 (1H, s), 8.25 (1H, br s). Compound **2l**, ^{1}H NMR ($CDCl_3$) δ: 1.22 (9H, s), 2.04 (3H, s), 7.45 (1H, d, $J = 9.0$ Hz), 7.54 (1H, s), 8.08 (1H, d, $J = 9.0$ Hz), 8.22 (1H, br s). Compound **2m**, ^{1}H NMR ($CDCl_3$) δ: 1.27 (9H, s), 2.19 (3H, s), 3.43 (1H, s), 7.08 (1H, d, $J = 8.5$ Hz), 7.17 (1H, s), 8.17 (1H, br s), 8.23 (1H, d, $J = 8.5$ Hz). Compound **2n**, ^{1}H NMR ($CDCl_3$) δ: 1.22 (6H, d, $J = 7.0$ Hz), 1.25 (9H, s), 2.17 (3H, s), 2.77 (1H, sept, $J = 7.0$ Hz), 6.98 (1H, d, $J = 8.0$ Hz), 7.08 (1H, s), 8.19–8.23 (2H, m). Compound **2o**, ^{1}H NMR ($CDCl_3$) δ: 1.26 (6H, d, $J = 7.0$ Hz), 1.31 (9H, s), 2.82 (1H, sept, $J = 7.0$ Hz), 7.25 (1H, t, $J = 7.0$ and 8.0 Hz), 7.33 (1H, t, $J = 7.0$ and 8.0 Hz), 7.57 (1H, d, $J = 8.0$ Hz), 7.68 (1H, d, $J = 8.0$ Hz), 7.80 (1H, s), 8.44 (1H, br s), 8.85 (1H, s).
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