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Tetrahedron Letters 49 (2008) 1768–1770
Tetrahedron Letters

A mild preparation of substituted indolizines and indole from simple aromatic precursors using (trimethylsilyl)diazomethane

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Received 24 October 2007; revised 5 January 2008; accepted 14 January 2008
Available online 19 January 2008

Abstract

A mild and convenient synthesis of substituted indolizines from readily available 2-(pyridin-2-yl)acetyl derivatives using (trimethylsilyl)diazomethane is described. The extension of this methodology to the synthesis of indole from 2-aminobenzaldehyde is also reported.

The indolizine ring system is an important heterocycle commonly used by medicinal chemists in their drug-design efforts. Indolizine-derived compounds have been reported to be L-type calcium channel blockers,[1] leukotriene synthesis inhibitors,[2] histamine H3 receptor antagonists,[3] 5-HT1A receptor ligands,[4] and phosphodiesterase V inhibitors[5] (Fig. 1).

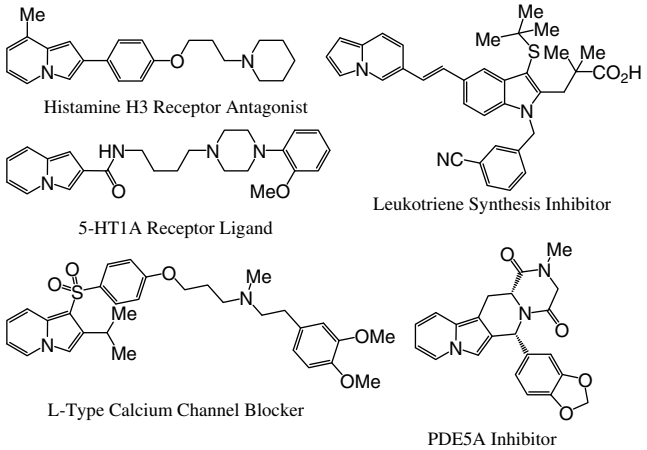
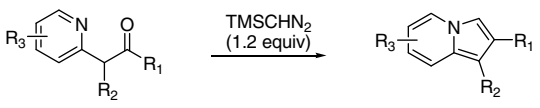


Fig. 1.

The synthesis of indolizine compounds has recently been reviewed.[6] Currently, several condensation reactions, 1,3-dipolar cycloadditions, and 1,5-dipolar cyclizations are known to facilitate the formation of these heterocycles.[6,7] Perhaps the most widely utilized method is the Tschitschibabin synthesis, in which a quaternary pyridinium halide, resulting from the reaction of a 2-substituted pyridine with an α-halo carbonyl compound, undergoes intramolecular condensation to deliver an indolizine product.[8] Unfortunately, many classical methods for indolizine construction, such as the Tschitschibabin reaction, require elevated temperatures and/or extended reaction times and, thus, may not be compatible with some functionality. In this Letter, we report a mild synthesis of substituted indolizines (**2**) from readily available 2-(pyridin-2-yl)acetyl derivatives (**1**) using (trimethylsilyl)diazomethane (Scheme 1). Addition of the lithium salt of (trimethylsilyl)diazomethane to ketones and aldehydes to generate indoles and cyclopentenes through carbene intermediates has been previously described.[9] However, to our knowledge this



1 **2**

Scheme 1.

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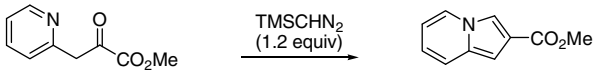
doi:10.1016/j.tetlet.2008.01.067

Letter represents the first report of the addition of (trimethylsilyl)diazomethane to carbonyl compounds to generate indolizines.

Typical reaction conditions involve the treatment of a 0.1 M solution of the 2-(pyridin-2-yl)acetyl substrate (1 equiv) with (trimethylsilyl)diazomethane (1.2 equiv) at room temperature in a vial open to air. The effects of solvent on the rate and yield of the reaction were evaluated using ketoester **3** as a model substrate, and the results are summarized in Table 1. Aprotic solvents of different polarities, such as CH_2Cl_2, CH_3CN, THF, DMF, and DMSO, and protic solvents, such as MeOH, EtOH, and *i*-PrOH, were examined. In general, the reactions were clean, and no products other than unreacted starting material were identified. It was noted that protic solvents were significantly preferred over aprotic solvents and that the reaction was fastest in MeOH. When carried out in EtOH and *i*-PrOH, the reaction afforded some transesterified indolizine byproducts, the yields of which are given in parentheses below.

The versatility of the reaction was evaluated using 2-(pyridin-2-yl)acetyl derivatives with modifications at the pyridyl ring and at the acetyl moiety (Table 2). Substrates with ester (**4**, **8**, and **9**), alkyl (**5**, **10**), aryl (**6**), and heteroaryl (**7**) substituents at R_1 afforded indolizine products in moderate to good yields (41–84%).[10–12] Compound **10** demonstrates that alkyl substitution is also tolerated at R_2 and that R_2 and R_1 can be linked to efficiently furnish a tricyclic ring system (72%). 2-(Pyridin-2-yl)acetyl derivatives bearing methoxy (**8**) and benzyloxy (**9**) substituents on the pyridyl ring were also smoothly converted to indolizine products (81% and 64%, respectively), demonstrating further that substitutions at the pyridyl ring are tolerated. In fact, the pyridyl moiety can be replaced by quinoline (**11**) without significantly affecting the reaction yield (Scheme 2).

Table 1
Solvent effects

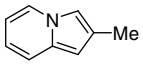
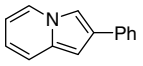
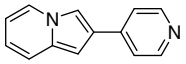
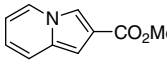
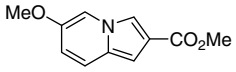
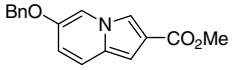
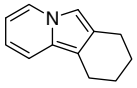


3 **4**

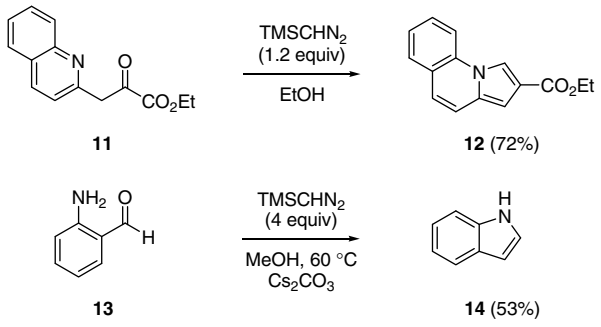
Solvent	% Yield[a,b] of **4**			
	0.5 h	2 h	6 h	24 h
CH_2Cl_2	0	0	0	0
CH_3CN	1	2	2	10
THF	0	1	2	2
DMF	0	4	6	6
DMSO	0	0	0	0
MeOH	94	93	92	94
EtOH	11(22)	34(34)	37(41)	46(44)
i-PrOH	8(2)	19(4)	47(9)	83(11)

[a] Reactions were carried out at 0.3 mmol substrate in 5 mL solvent with 1.2 equiv of $TMSCHN_2$ (2 M in Et_2O) at ambient temperature.
[b] Yields are based on reverse-phase HPLC analysis compared to an analytical sample.

Table 2
Substituents tolerability

Entry	Product	Yield[a,b] (%)
5		67
6		57
7		41
4		84
8		81
9		64
10		63

[a] Reactions were carried out at 1 mmol substrate in 10 mL of methanol with 1.2 equiv of $TMSCHN_2$ (2 M in Et_2O) at ambient temperature.
[b] Yields are for isolated product after a reaction time of 24 h and are unoptimized.[14]



Scheme 2.

In light of the mild conditions and operational simplicity of our indolizine synthesis, we sought to extend the described protocol to the preparation of other heterocycles. Having noted both the presence and proximity of nucleophilic and electrophilic moieties in the 2-(pyridin-2-yl)-acetyl derivatives discussed above, we hypothesized that similarly disposed bifunctional molecules might also prove amenable substrates for heterocycle formation. We were, thus, pleased to discover that 2-aminobenzaldehyde (**13**), a bifunctional substrate, could be converted to indole (**14**, Scheme 2) in moderate yield. While the rate of indole formation was slower than that typically observed for the indolizine derivatives described in this Letter, efficient conversion was achieved at 60 °C using 4 equiv of

(trimethylsilyl)diazomethane and 2 equiv of Cs_2CO_3 as an alkaline additive.[13] The utility of this method for the synthesis of functionalized indoles is currently under investigation and will be reported in due course.

In conclusion, we have developed a mild and convenient method for the synthesis of substituted indolizines from readily available 2-(pyridin-2-yl)acetyl derivatives using (trimethylsilyl)diazomethane in moderate to good yields (41–84%). We have further demonstrated that this reaction can be applied to the synthesis of indole from 2-aminobenzaldehyde and are currently evaluating the feasibility of this synthetic construct for the preparation of substituted indoles and other heterocycles.

References and notes

1. Gupta, S. P.; Mathur, A. N.; Nagappa, A. N.; Kumar, D.; Kumaran, S. *Eur. J. Med. Chem.* **2003**, *38*, 867–873.
2. Hutchinson, J. H.; Therien, M.; Frenette, R. (Bicyclic azaarylmethoxy)indoles as inhibitors of leukotriene biosynthesis. Eur. Pat. Appl. EP542355, 1993.
3. Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767–1770.
4. Gmeiner, P.; Huebner, H.; Bettinetti, L.; Schlotter, K. Preparation of 2-indolizinecarboxamides and related compounds as central nervous system agents. PCT Int. Appl. WO 015737, 2006.
5. Orme, M. W.; Sawyer, J. S.; Schultze, L. M. Preparation of heterocycles containing a pyrido[1,2-*a*]pyrazinedione subunit for therapeutic use as phosphodiesterase V inhibitors. PCT Int. Appl. WO 000657, 2002.
6. Shipman, M. *Sci. Synth.* **2001**, *10*, 745–787.
7. (a) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547–4550; (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463–4466; (c) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433–3436; (d) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863–6867; (e) Przewloka, T.; Chen, S.; Xia, Z.; Li, H.; Zhang, S.; Chimmanamada, D.; Kostik, E.; James, D.; Koya, K.; Sun, L. *Tetrahedron Lett.* **2007**, *48*, 5739–5742; (f) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050–12051; (g) Tewarl, R. S.; Bajpal, A. *J. Chem. Eng. Data* **1985**, *30*, 505–507; (h) Zhou, J.; Hu, Y.; Hu, H. *Synthesis* **1999**, 166–170.
8. Bragg, D. R.; Wibberley, D. G. *J. Chem. Soc.* **1963**, 3277–3281.
9. (a) Lee, H.-Y.; Kim, W.-Y.; Lee, S. *Tetrahedron Lett.* **2006**, *48*, 1407–1410; (b) Hari, Y.; Kanie, T.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1137–1139; (c) Taber, D. F.; Plepys, R. A. *Tetrahedron Lett.* **2005**, *46*, 6046–6047; (d) Miyagi, T.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 6303–6305; (e) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2000**, *41*, 6859–6863.
10. Substrate **5** (1-pyridin-2-yl-propan-2-one) was purchased from ChemBridge Corp., San Diego, CA, USA. Substrates **10** (2-(2-pyridinyl)cyclohexanone) and **11** (2-oxo-3-quinolin-2-yl-propionic acid ethyl ester) was purchased from Ryan Scientific Inc., Isle of Palms, SC, USA.
11. Substrate **6** (1-phenyl-2-(pyridin-2-yl)ethanone) was prepared in a manner similar to: Goldberg, N. N.; Barkley, L. B.; Levine, R. *J. Am. Chem. Soc.* **1951**, *73*, 4301–4303; Substrate **7** (2-(pyridin-2-yl)-1-(pyridin-4-yl)ethanone) was prepared in a manner similar to: Goldberg, N. N.; Levine, R. *J. Am. Chem. Soc.* **1952**, *74*, 5217–5219.
12. Typical procedure for the preparation of substrates **4** (methyl 2-oxo-3-(pyridin-2-yl)propanoate), **8** (methyl 3-(6-methoxypyridin-2-yl)-2-oxopropanoate), and **9** (methyl 3-(6-(benzyloxy)pyridin-2-yl)-2-oxopropanoate): Lithium diisopropylamide (33.5 mL of 1.5 M in heptane/tetrahydronfuran/ethylbenzene, 50.2 mmol) was added dropwise at −78 °C under nitrogen to a solution of 2-picoline (2.33 g, 25.1 mmol) in THF (100 mL). The mixture was stirred for 15 min and methyl 2,2,2-trimethoxyacetate (4.56 g, 27.6 mmol) was added in 5 mL of THF. The mixture was stirred at −78 °C for 60 min. The mixture was then allowed to warm to room temperature and stir for another 60 min. The mixture was poured into 1 M HCl (200 mL) and stirred at room temperature for 45 min. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with Et_2O (200 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography (silica gel, 1:3 EtOAc/hexane) to obtain 3.67 g of substrate **4**, 82%. Substrates **8** and **9** were obtained in 58% and 37%, respectively.
13. *Procedure for the synthesis of indole* (**14**) *from 2-aminobenzaldehyde*: To a homogeneous solution of 2-aminobenzaldehyde (0.200 g, 1.65 mmol) and cesium carbonate (1.08 g, 3.30 mmol) in MeOH (8.5 mL) was added (trimethylsilyl)diazomethane (2.0 M in ether, 3.30 mL, 6.60 mmol) dropwise over 10 min at 60 °C. The mixture was stirred for 30 min at 60 °C, cooled to room temperature, quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The organics were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel flash chromatography (0–15% EtOAc/hexane) to afford indole (0.102 g, 53%) as a crystalline solid. Spectroscopic properties of the synthetic material matched those of an authentic sample.
14. *Procedure for the synthesis of methyl indolizine-2-carboxylate* (**4**) *from methyl 2-oxo-3-(pyridin-2-yl)propanoate.* Trimethylsilyldiazomethane (2.0 M in diethyl ether, 0.6 mL, 1.2 mmol) was added slowly to a solution of methyl 2-oxo-3-(pyridin-2-yl)propanoate (0.179 g, 1.0 mmol) in methanol (10 mL). The reaction was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (silica gel, 1:2 EtOAc/hexane) to afford **4** as a white solid (0.147 g, 84%). ^1H NMR, MS, and CHN-analysis were consistent with the structure, mp: 96–97 °C (recrystallized from 10% v/v EtOAc/hexane, uncorrected; lit. 99–100 °C from hexane).