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NOVEL SYNTHESIS OF PYRROLO[2,1-*a*]-ISOQUINOLINE USING THE REACTION OF ISOQUINOLINIUM SALTS WITH ACTIVE METHYLENE COMPOUNDS

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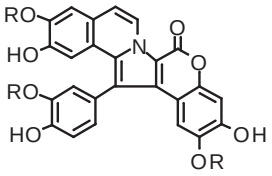
Abstract —— 2-Alkyl-1-methylthioisoquinolinium salts were easily prepared from 2-alkyl-1(2*H*)-isoquinolones *via* 2-alkyl-1(2*H*)-thioisoquinolones in two steps. Under mild conditions, the reaction of 2-alkyl-l-methylthioisoquinolinium salts with active methylene compounds in the presence of sodium hydride afforded 2-alkyl-1-(substituted methylene)isoquinolines in good yields. The cyclizationof 2-benzylisoquinolines using acetic anhydride produced the pyrrolo[2,1-*a*]-isoquinolines. Further, the reaction of 1-chloro-2-phenacylisoquinolinium salt with active methylene compounds afforded the pyrrolo[2,1-*a*]isoquinolines in one pot.

Various methods for the synthesis of indolizine derivatives have been reported.[1] Recently, Iwao *et al*. reported the novel total synthesis of the marine alkaloid lamellarins containing the pyrrolo[2,1-*a*]isoquinoline skeleton (Scheme 1).[2] Therefore, the functionalized pyrrolo[2,1-*a*]isoquinolines are very useful synthetic intermediate for them. The conventional methods for preparing the substituted pyrrolo[2,1-*a*] isoquinoline derivatives are *a*) Michael condensation of Reissert compounds,[3] and *b*) 1,3- and 1,5-dipolar cycloaddition reactions.[4,5] In this communication, we report a novel method for the synthesis of a pyrrolo[2,1-*a*]isoquinoline skeleton using the cyclization of 2-alkyl-1-(substituted methylene)isoquinolines, which were easily prepared from the reaction of 2-alkyl-1-methylthioisoquinolinium iodides with active

methylene compounds such as dimethyl malonate, malononitrile, methyl cyanoacetate, and 1,3-cyclohexanedione, and the cyclization of 1-chloro-2-phenacylisoquinolinium salt with active methylene compounds using sodium hydride as a base.

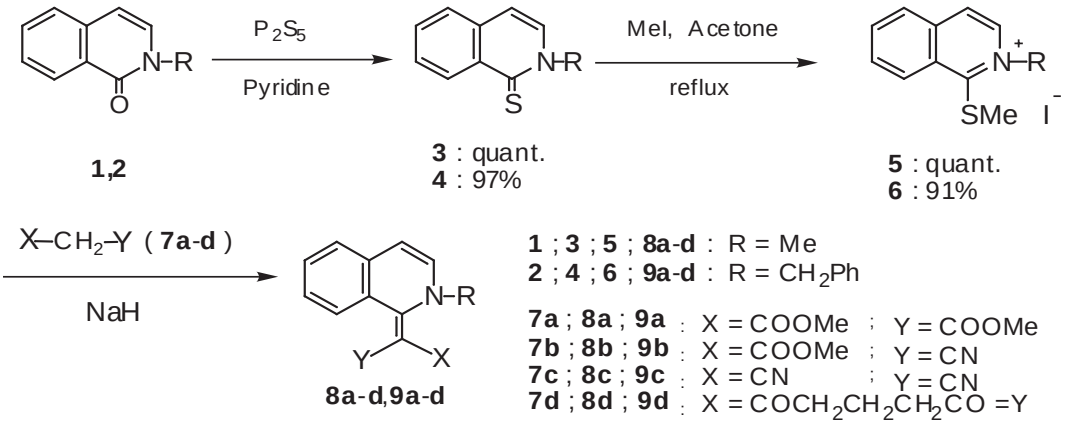


R = Me lamellarin D
R = H lamellarin H

Scheme 1

Reaction of 1-Methylthioisoquinolinium Salts with Active Methylene Compounds

First, the reaction of active methylene compounds with isoquinolinium salts having a methylthio group as a leaving group at position-1 was examined under milder conditions in the presence of sodium hydride (Scheme 2 and Table 1). 2-Methyl- and 2-benzyl-1(2*H*)-thioisoquinolone (**3** and **4**) were prepared from 2-methyl- and 2-benzyl-1(2*H*)-isoquinolones (**1** and **2**) in excellent yields. The reaction of thioisoquinolone (**3** and **4**) with methyl iodide afforded 2-methyl- and 2-benzyl-1-methylthioisoquinolinium iodides (**5** and **6**) in 99 and 91% yields, respectively. The reaction of 2-methylisoquinolinium iodide (**5**) with straight-chain active methylene compounds (**7a-c**) in the presence of sodium hydride for 1.5 h at room temperature afforded 2-methyl-1-(substituted methylene)isoquinolines [**8a** (88%), **8b** (81%), and **8c** (85%)]. Further, the reaction of **5** with cyclic active methylene compound (**7d**) at 90 ℃ for 6 h gave 2-methyl-1-(substituted methylene)isoquinoline (**8d**) in 92% yield. Similarly, the reaction of 2-benzylisoquinolinium iodide with **7a-d** produced 2-benzyl-1-(substituted methylene)isoquinolines [**9a** (95%), **9b** (98%), **9c** (99%), and **9d** (96%)]. Nuclear Overhauser and exchange spectroscopies of **8b** and **9b** showed that the methyl group in the ester group correlated to the *N*-methyl or *N*-methylene group. Thus, the stereochemistries between the ester and the *N*-substituted groups in **8b** and **9b** were suggested to be Z-form. This type of reaction is regarded as a promising method for the carbon-carbon bond forming reaction at position-1 in the

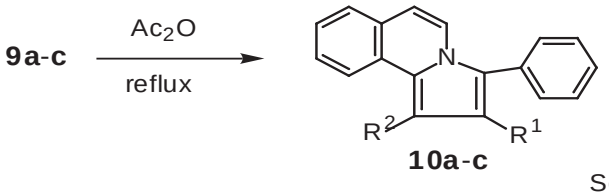


Scheme 2

Table 1. Reaction of Isoquinolinium Salt with Active Methylene Compounds

Entry	Temp. (°C)	Time (h)	Solvent	X	Y	Product	Yield (%)
1	rt	1.5	THF	COOMe	COOMe	**8a**	88
2	rt	1.5	THF	CN	COOMe	**8b**	81
3	rt	1.5	THF	CN	CN	**8c**	85
4	90	6	DMF	$COCH_2CH_2CH_2CO$		**8d**	92
5	rt	2	THF	COOMe	COOMe	**9a**	95
6	rt	2	THF	CN	COOMe	**9b**	98
7	rt	2	THF	CN	CN	**9c**	99
8	rt	2	DMF	$COCH_2CH_2CH_2CO$		**9d**	96

isoquinoline ring. Next, we attempted cyclization of 2-benzyl compounds (**9a-d**) in acetic anhydride to provide the pyrrolo[2,1-*a*]isoquinoline derivatives functionalized (Scheme 3). Heating of **9a-c** in acetic anhydride at 130 °C for 4 h afforded the corresponding pyrrolo[2,1-*a*]isoquinolines [**10a** (91%), **10b** (98%), and **10c** (12%)]. Unfortunately, cyclization of **9d** did not give pyrrolo[2,1-*a*]isoquinoline with decomposition of **9d**. Cyclization of **9a**,**b** having the ester group smoothly proceeded to afford **10a**,**b**.



10a : R^1 = OCOMe ; R^2 = COOMe ; 91%
10b : R^1 = OCOMe ; R^2 = CN ; 98%
10c : R^1 = NH_2 ; R^2 = COOH ; 12%

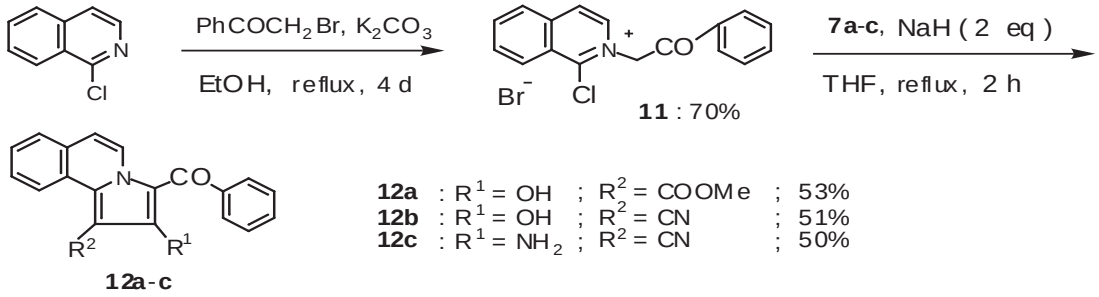
Scheme 3

Cyclization of 1-Chloroisoquinolinium Salt with Active Methylene Compounds

Moreover, cyclization of 2-phenacylisoquinolinium bromide (**11**) bearing the chloro group as a leaving group at position-1 was examined (Scheme 4). Isoquinolinium salt (**11**) was easily prepared from 1-chloroisoquinoline with phenacyl bromide in the presence of potassium carbonate as a base in 70% yield. The THF suspensions of isoquinolinium salt (**11**) and **7a-c** in the presence of sodium hydride (2 eq) refluxed for 5 h to give successfully the corresponding pyrrolo[2,1-*a*]isoquinolines functionalized [**12a** (53%), **12b** (51%), and **12c** (50%)] in one step. The structures of all new compounds (**5**,**6**,**8a-d**,**9a-d**, **10a-c**, and **12a-c**) were confirmed by IR, ^{1}H-NMR and MS spectral analyses.[6)]

In conclusion, a novel reaction of active methylene compounds with isoquinolinium salts having a methylthio group as a leaving group at position-1 gave the 2-alkyl-1-(substituted methylene)isoquinolines under mild condition in fairly good yields. Cyclization of 2-benzyl compounds having the ester group in acetic anhydride produced the pyrrolo[2,1-*a*]isoquinolines in excellent yields. Moreover, reaction of 1-chloro-2-phenacylisoquinolinium salt with active methylene compounds successfully afforded the pyrrolo-

[2,1-*a*]isoquinolines in one pot. Further applications and modifications of the methodology are in progress.



Scheme 4

REFERENCES AND NOTES

1. M. Iwao, and T. Kuraishi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 297 ; Review for synthesis of pyrrolo[2,1-*a*]isoquinolines : T. Uchida, and K. Matsumoto, *Synthesis*, **1976**, 209.

2. F. Ishibashi, Y. Miyazaki, and M. Iwao, *Tetrahedron*, 1997, **53**, 5951; N. Lindquist, W. Fenical, G. D. Van Duyne, and J. Clardy, *J. Org. Chem.*, 1988, **53**, 4570; A. R. Carroll, B. F. Bowden, and J. C. Coll, *Aust. J. Chem.*, 1993, **46**, 489.

3. V. Boekelheide, and J. C. Godfrey, *J. Am. Chem. Soc.*, 1953, **75**, 3679

4. R. Husgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, **1963**, 1441; Y. Kobayashi, I. Kumadaki, Y. Sekine, and T. Kutsuma, *Chem. Pharm. Bull.*, 1973, **21**, 1118; N. S. Basketter, and A. O. Plunkett, *J. Chem. Soc., Chem. Comm.*, **1973**, 188.

5. F. Krohnke, and W. Zecher, *Chem. Ber.*, 1962, **95**, 1128.

6. Representative data for **8a** : yellow crystalline powder, mp 237-239 ℃; IR (Nujol): 1720, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 6H), 4.15 (s, 3H), 7.50-8.00 (m, 5H), 8.35-8.60 (m, 1H); MS *m/z*: 273 (M^+); Anal. Calcd for $C_{15}H_{12}NO_4$: C; 65.92; N, 5.13; H, 5.53. Found: C, 65.66; N, 5.40; H, 5.27. **9a**: red plates, mp 239 ℃; IR (Nujol): 1701, 1595, 758; ^{1}H-NMR ($CDCl_3$) δ 3.63 (s, 6H), 5.72 (s, 2 H), 7.25 (dd, *J* =2.0, 6.6 Hz, 2H), 7.23 (s, 5H), 7.32-7.39 (m, 3H), 7.58 (d, *J* =7.0 Hz, 1H), 7.72-7.88 (m, 4H), 8.60 (d, *J*= 8.2 Hz, 1H); MS *m/z*: 349 (M^+); Anal. Calcd for $C_{21}H_{19}NO_4$: C; 72.19; N, 4.01; H, 5.48. Found: C,72.49; N, 3.80; H, 5.61. **10a**: yellow needles, mp 165-166 ℃; ^{1}H-NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.95 (s, 3H), 6.93 (d, *J* =7.4 Hz, 1H), 7.45-7.60 (m, 8H); MS *m/z*: 359 (M^+) ; Anal. Calcd for $C_{22}H_{17}NO_4$: 359.1158. Found: 359.1187. **12b**: yellow crystalline powder, mp 219-222 ℃; IR (Nujol): 3187, 3136, 2217, 1665, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.98 (d, *J* =7.3 Hz, 1H), 7.55-7.71 (m, 8H), 7.93 (d, *J* =7.3 Hz, 1H), 8.92-8.94 (m, 1H); MS *m/z*: 312 (M^+); Anal. Calcd for $C_{15}H_{12}NO_4$: 312.0899. Found: 312.0862.