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Solvent-Free Cycloaddition Reaction of 3-Indolylimines with Chloroacetyl Chloride Under Microwave Irradiation

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ABSTRACT: *Solvent-free approach is developed for the rapid synthesis of spiro[azetidine-indoles]* **6a–g** *on basic alumina supported potassium carbonate (K_2CO_3–Al_2O_3) from the cycloaddition reaction of indolylimines* **3** *and chloroacetyl chloride* **4** *as synthons using microwaves. The procedure neither required toxic and hazardous base nor volatile solvents.* **3** *was synthesized in situ by the neat reaction of indole-2,3-diones* **1** *and fluorinated anilines* **2** *under microwave irradiation. Solvent-free aminoalkylation of spiro compounds* **6a** *and* **6b** *has been carried out under microwaves.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:468–473, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10180

INTRODUCTION

The β-lactam heterocycles are the most prescribed antibiotics used in medicine [1], and various biological activities are possessed by 3-chloromonocyclic β-lactams [2,3]. They also function as enzyme inhibitors and are effective on the central nervous system [4]. Moreover, 3-spiro indoline moieties also play a vital role largely due to the wide range of biological activities associated with them and their presence in biodynamic indole alkaloids [5,6]. Spiro[azetidineindoles] have also shown unique antimicrobial action [7]. It has been observed that introduction of a fluorine atom or CF_3 group to heterocycles may act as a pharmacophore enhancing pharmacological properties of the compounds as compared to their non-fluorinated analogues [8]. Incorporation of fluorine atoms into the indole ring tends to increase drug persistence by increasing the solubility of the drug in lipoid material and fat deposits in body [9].

RESULTS AND DISCUSSION

Conventional synthesis of spiro-azetidines involves a long and tedious (80–82 h) two-step procedure that uses dry benzene/dioxane as solvent and triethylamine as basic catalyst, giving a product in just 55–63% yield [7,10]. The synthesis of β-lactams under microwave irradiation using the MORE (microwave-induced organic reaction enhancement) technique was extensively studied by Bose et al. [11], using *N*-methyl morpholine as basic catalyst in place of triethylamine and chlorobenzene/DMF as a energy transfer media. However, microwave-enhanced chemical reactions on inorganic solid supports under solventless conditions have attracted attention recently [12]. The advantages of these methods are enhanced reaction rates, milder reaction conditions, easier work-up, and organic syntheses are carried out in open vessels with ecofriendly conditions on a preparative scale.

To the best of our knowledge there is no report on solvent-free synthesis of spiro[azetidineindoles].

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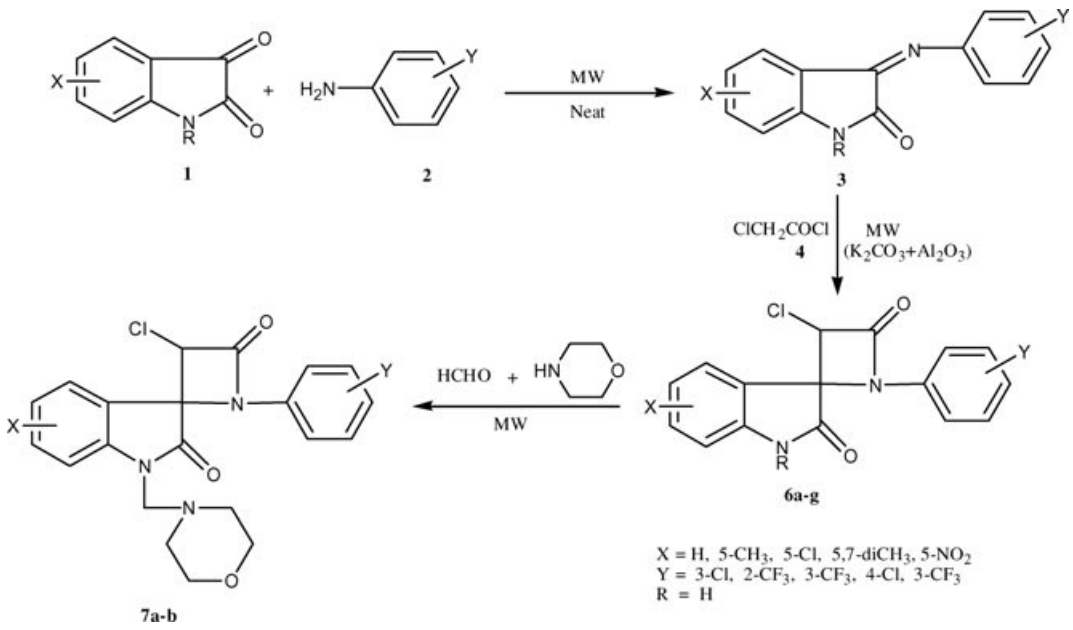
Hence in view of our interest on the synthesis of biodynamic heterocycles and fluorine containing 3-spiro indolines using nonconventional method of organic synthesis [13], we report here the solvent-free synthesis of a series of new fluorinated spiro[azetidine-indole]diones **6** by the cycloaddition reaction of 3-arylimino indolinones **3** with chloroacetyl chloride **4**, using basic alumina-supported potassium carbonate (K_2CO_3–Al_2O_3) as inorganic support under microwave irradiation. The intermediates **3a–g** were synthesized in situ by the neat reaction of indole-2,3-diones **1** and substituted anilines **2** under microwave irradiation in 30–50 s without using any support or catalyst.



1 2 3 6a-g 7a-b

Earlier reports mentioned the variable formation of cis and trans isomers of β-lactams [14,11a,c] depending on the power level of microwave irradiation or order of addition of reactants in conventional synthesis, which was rationalized on the basis of change of mechanism under a given set of reaction conditions. Recently, we have also reported the effect of power level on diastereoselective synthesis of spiro oxirans [15]. Encouraged by this, we have studied the title cycloaddition reaction under different conditions of conventional and microwave-mediated synthesis using either triethylamine or K_2CO_3 as basic catalyst respectively. However, present studies showed exclusive formation of only one diastereomer irrespective of different variables as shown in Table 1.

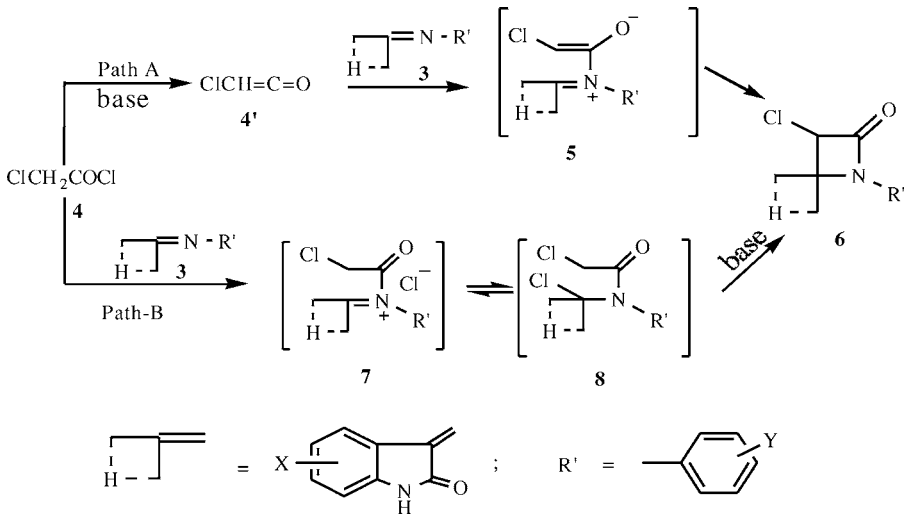
Comparative studies (Table 1) showed that the reaction occurred successfully when basic alumina-supported potassium carbonate was used as support, eliminating the requirement of volatile solvent and hazardous base triethylamine. In such cases the basicity of alumina (basic) is not sufficient to cause cycloaddition as observed by earlier workers for the synthesis of other β-lactams [16].

TABLE 1 Comparative Study for the Synthesis of **6a** Using (A) Classical Method, (B) Microwave Irradiation (MW), (C) Conventional Heating (Using Thermostated Oil Bath)

Method	*Medium/Support*	*MW Power (W)*	*Time*	*Temp[a] (°C)*	*Yield[b] (%)*
A	Triethylamine + dry benzene	–	82 h	40–45	61
B	(i) *o*-Dichlorobenzene + triethylamine	275	10 min	154–156	78
	(ii) *o*-Dichlorobenzene + triethylamine	480	7 min	154–156	76
	(iii) Basic alumina	640	25 min	135–137	Nil
	(iv) K_2CO_3–Al_2O_3	640	6 min	138–140	90
C	K_2CO_3–Al_2O_3	–	6 min	138–140	30

[a]The final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture.
[b]Yield of the isolated product.

Two mechanistic pathways A and B by which imines **3** and acid chloride **4** combine to form β-lactams have been proposed [17]. Path A involves prior formation of ketene **4′** by the reaction of acid chloride with base and subsequent cycloaddition with imine (the Staudinger reaction), perhaps via zwitterionic intermediate **5**, and path B involves direct acylation of the imine with the acid chloride giving *N*-acyliminium chloride **7**, which may be in equilibrium with chloro amide **8**. Reaction of **7** or **8** with base then gives β-lactams **6**.



However, in the present investigation, the title reaction proceeds via path A, which is confirmed by IR spectral studies carried out during monitoring the progress of reaction [17]. A strong band at 2290 cm^{-1} is assigned to intermediate ketene **4′** which is well resolved from carbonyl bands of acid chloride (1800 cm^{-1}) and the β-lactams **6** (1730 cm^{-1}), leading to formation of only one diastereomer.

The identification of spiro compounds is based on their spectral studies and elemental analyses (Tables 2 and 3). IR spectra of compounds **6a–g** showed characteristic absorption bands at the region of 3260–3230, 1730–1725, and 1700–1690 cm^{-1} due to NH and two carbonyl groups. The ^1H NMR spectra of products **6a–g** showed signals at δ 4.27–4.30 (s, Cl—CH) along with aromatic protons at 7.06–7.89 (m, Ar-H) and NH protons at δ 8.34–8.41 (bs, 1H, NH exchangeable with D_2O).

Formation of the spiro product was further confirmed on the basis of ^{13}C, ^{19}F NMR, and mass spectra. In the ^{13}C NMR spectrum of **6a**, sharp signals were observed at δ 175.3 (C=O), 163.8 (C=O), 145.1, 143.3, 139.81, 138.2, 137.1, 136.5, 135.5, 134.2, 130.5, 129.1, 125.1, 119.6 (12 aromatic carbons), 83.5 (spiro carbon), and 42.8 (Cl—CH).

In the mass spectrum of **6a**, the appearance of molecular ion peak *m/z* (M^+) at 380 and at 382 ($M^+ + 2$) due to chlorine isotopic peak showed the formation of spiro compound. The presence of fluorine in all synthesized compounds was confirmed by ^{19}F NMR spectra. Single fluorine attached to the indole

TABLE 2 Physical and Analytical Data of **6a–g** and **7a–b**

	X	Y	Time (min)	m.p. (°C)	Yield (%)	R_f [a]	Molecular Formula	Analysis (%): Calcd (Found) C	N
6a	5-CH3	2-CF_3	6	172	92	0.61	$C_{18}H_{12}ClF_3N_2O_2$	56.78 (56.92)	7.36 (7.33)
6b	5-Cl	3-Cl	6	158	90	0.54	$C_{16}H_9Cl_3N_2O_2$	52.28 (52.09)	7.62 (7.58)
6c	5,7-diCH_3	2-CF_3	7	160	91	0.53	$C_{19}H_{14}ClF_3N_2O_2$	57.81 (57.62)	7.10 (7.07)
6d	5-F	3-CF_3	6	95	88	0.63	$C_{17}H_9ClF_4N_2O_2$	53.07 (52.93)	7.28 (7.24)
6e	5-Cl	2-CF_3	7	75	91	0.62	$C_{17}H_9Cl_2F_3N_2O_2$	50.90 (50.79)	6.98 (6.95)
6f	5-NO_2	3-Cl	8	98	85	0.58	$C_{16}H_9Cl_2N_3O_4$	50.82 (50.68)	11.11 (11.07)
6g	H	3-CF_3, 4-Cl	7	190	89	0.61	$C_{17}H_9N_2O_2Cl_2F_3$	50.90 (50.76)	6.98 (7.02)
7a	5-CH_3	2-CF_3	3	212	86	0.69	$C_{23}H_{21}F_3ClN_3O_3$	57.57 (57.35)	8.76 (8.73)
7b	5-Cl	3-Cl	4	223	89	0.61	$C_{21}H_{18}N_3O_3Cl_3$	54.04 (54.25)	9.00 (8.98)

[a]Using solvent system benzene/ethyl acetate (8:2).

TABLE 3 Infrared and ^{1}H NMR Data of Compounds **6a–g** and **7a–b**

	IR (cm^{-1})	*^{1}H NMR (δ, ppm)*	*^{19}F NMR (δ, ppm)*
6a	3250 (NH), 1725, 1695 (two C=O), 760 (C–Cl)	δ_H 2.25 (s, 3H, CH_3), 4.30 (s, 1H, CH–Cl), 7.06–7.89 (m, 7H, Ar–H), 8.38 (bs, 1H, NH)	−63.29 (s, CF_3)
6b	3240 (NH), 1730, 1690 (two C=O), 740 (C—Cl)	δ_H 4.28 (s, 1H, CH–Cl), 7.29–7.70 (m, 7H, Ar–H), 8.34 (bs, 1H, NH)	
6c	3230 (NH), 1730, 1698 (two C=O), 765 (C—Cl)	δ_H 2.15 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.29 (s, 1H, CH–Cl), 7.31–7.76 (m, 6H, Ar–H), 8.40 (bs, 1H, NH)	−64.04 (s, CF_3)
6d	3250 (NH), 1725, 1693 (two C=O), 748 (C—Cl)	δ_H 4.28 (s, 1H, CH–Cl), 7.11–7.76 (m,7H, Ar–H), 8.39 (bs, 1H, NH)	−63.78 (s, CF_3) −119.52 (s, F)
6e	3245 (NH), 1728, 1697 (two C=O), 740 (C—Cl)	δ_H 4.30 (s, 1H, CH–Cl), 7.09–7.70 (m, 7H, Ar–H), 8.41 (bs, 1H, NH)	−64.78 (s, CF_3)
6f	3240 (NH), 1730, 1700 (two C=O), 740 (C—Cl)	δ_H 4.31 (s, 1H, CH–Cl), 7.18–7.71 (m, 7H, Ar–H), 8.39 (bs, 1H, NH)	
6g	3250 (NH), 1727, 1698 (two C=O), 760 (C—Cl)	δ_H 4.28 (s, 1H, CH–Cl), 7.09–7.70 (m, 7H, Ar–H), 8.40 (bs, 1H, NH)	−62.98 (s, CF_3)
7a	1730, 1690 (two C=O), 1180 (C–O–C), 1460, 750	δ_H 2.20 (s, 3H, CH_3), 2.70–2.83 (t, 4H, $N(CH_2)_2$), 3.40–3.55 (t, 4H, $O(CH_2)_2$), 4.12 (s, 2H, N–CH_2–N) 4.34 (s, 1H, CH–Cl), 6.98–7.91 (m, 7H, Ar–H)	−64.25 (s, CF_3)
7b	1728, 1690 (two C=O), 1180 (C–O–C), 1450, 770	δ_H 2.71–2.85 (t, 4H, $N(CH_2)_2$), 3.41–3.56 (t, 4H, $O(CH_2)_2$), 4.17 (s, 2H, N–CH_2–N), 4.38 (s, 1H, CH–Cl), 7.05–7.76 (m, 7H, Ar–H)	

Note: IR spectra were obtained in KBr disc; NMR spectra were obtained in $CDCl_3$ solution.

ring and the CF_3 group attached to the phenyl ring appeared as singlets at δ −119.52 and −62.98 to −64.78 ppm, respectively.

Further, in view to improve bioactivity, aminoalkylation of spiro compounds **6a** and **6b** were carried out under microwave irradiation. Under a conventional manner, it requires several hours of heating, using organic solvents. Faced with this dilemma, we explored a more effective and much faster route (lasting a few minutes) for the implementation of aminoalkylation of the spiro compounds in solvent-free conditions.

Aminoalkylation occurs exclusively at indole nitrogen, and formation of mannich base from the corresponding spiro compound has been confirmed by appearance of new resonance signals centered at δ 2.71–2.85, 3.40–3.56, and 4.12–4.17 ppm in ^{1}H NMR spectrum because of morpholino group.

EXPERIMENTAL

Melting points were determined on a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer Infracord spectrophotometer model 577 (ν_{max} in cm^{-1}), ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker-DRX-300 spectrometer using $CDCl_3$ as a solvent at 300.13, 75.47, and 282.37 MHz, respectively. TMS was used as internal reference for ^{1}H and ^{13}C NMR and TFA as external reference for ^{19}F NMR. Mass spectrum of the representative compound **6a** was recorded on a Kratos-30 spectrometer. Elemental analyses for C and N were performed on a Heraeus Carlo Erba 1108 analyzer and found within ±3% of theoretical value. Progress of the reaction was monitored by TLC using silica gel "G"-coated glass plates and benzene/ethyl acetate (8:2) as eluent. The microwave-induced reactions were carried out in a BMO-7OOT modified domestic oven fitted with a condenser and a magnetic stirrer. Indole-2,3-diones were prepared according to the literature procedures [18]. Inorganic solid support (K_2CO_3–Al_2O_3) was used immediately after activation under microwave irradiation.

3-Chloro-1-(2-trifluoromethylphenyl)-5′-methylspiro[azetidine-2,3′[3H]-indole]-2′,4(1′H)-dione(**6a**) was prepared by two routes: (1) conventional synthesis and (2) microwave-assisted procedure.

Conventional Synthesis

It involves two steps:

1. Synthesis of 3-(2-trifluoromethylphenyl)-imino-5-methyl-2H-indol-2-one (**3a**): An equimolar

mixture (0.01 mol) of 5-methyl-indole-2,3-dione **1a** and 2-trifluoromethyl aniline **2a** was refluxed in dry toluene for 4 h. Crystals separated out on cooling were dried and recrystallized from ethanol (yield = 70%; m.p. 165°C [19]).

2. Synthesis of spiro product: To a well stirred solution of **3a** (0.005 mol) and triethylamine (0.005 mol) in dry benzene (10 ml) was added chloroacetyl chloride (0.005 mol) dropwise at room temperature. After the addition of chloroacetyl chloride, the mixture was further stirred for 3 days. The precipitated triethylamine hydrochloride was filtered off and washed thoroughly with dry benzene. The solvent from the filtrate was evaporated in vacuo and the residue was recrystallized from benzene-pet-ether.

Microwave-Assisted Synthesis (Synthesis of **3a***)*

An equimolar mixture (0.01 mol) of **1a** and **2a** was irradiated under microwave irradiation for 30 s at 640 W (monitored by TLC). The intermediate **3a** was so obtained in reasonable purity (TLC) (confirmed by mixed mp with authentic sample), and used as such for the next step for the synthesis of spiro[indole-azetidine] **6a** by following two methods to study the role of power level, medium, and base.

Using the MORE technique: An equimolar mixture (0.005 mol) of **3a**, triethylamine, and chloroacetyl chloride in *o*-dichlorobenzene (5 ml) in an erlenmeyer flask was irradiated inside a domestic microwave oven at power 30% (275 W) and 70% (480 W) for 10 and 7 min respectively to check the effect of power level. Progress of the reaction was monitored by TLC. Reaction mixture was cooled down and the precipitate of triethylamine hydrochloride was filtered off and washed thoroughly with benzene, and the excess solvent was evaporated on a rotary-evaporator to give a solid that was found to be pure by TLC.

Using inorganic solid support: K_2CO_3 (2 mmol, i.e., 376 g) was coground with 4 g of basic alumina in an agate mortar. To this, a mixture of intermediate **3a** (2 mmol) and chloroacetyl chloride **4** (3 mmol) was added, mixed thoroughly, and irradiated under microwave irradiation at 640 W for 6 min. The product was obtained by desorption with methanol and found to be pure by TLC.

The identity of compound **6a** synthesized by various methods, i.e., conventionally and under microwave irradiation by changing power level, medium, and base, was confirmed by mixed mps and spectral studies. Other compounds **6b–g** listed in Table 2 were similarly prepared under solvent-free conditions using (K_2CO_3–Al_2O_3) as support.

Synthesis of Mannich Base of Spiro Compounds **7a/7b**

A mixture of appropriate spiro compound **6a/6b** (1 mmol), formaldehyde (1.5 mmol, 40%), and morpholine (1 mmol) was irradiated in a microwave oven at power output at 640 W for the period indicated in Table 2 (TLC). The resultant residue after crystallization from methanol gave **7a/7b**.

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