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Journal of Organometallic Chemistry 524 (1996) 87–93

Journal of Organometallic Chemistry

Organoiridium catalyzed hydrogen isotope exchange: ligand effects on catalyst activity and regioselectivity

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Received 30 January 1996; revised 18 March 1996

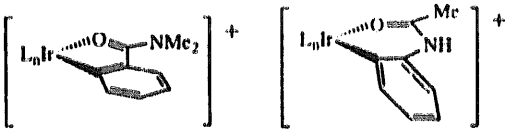
Abstract

Several iridium complexes $[Ir(cod)L_2]X$ (L = phosphine ligand) were used as precatalysts for the exchange labeling of a range of model compounds with deuterium gas. Complexes with monodentate L (e.g. $PMePh_2$, PPh_3 and substituted derivatives thereof) catalyzed exchange selectively of hydrogens four bonds away from a coordinative heteroatom in the substrate, while those with bidentate L (bis(diphenylphosphino)ethane (dppe) and bis(diphenylphosphino)butane) catalyzed exchange of hydrogens both four and five bonds away from a coordinative heteroatom. At heavier loadings, some monodentate complexes also catalyzed five-bond labeling of some substrates. $[Ir(cod)(dppe)]BF_4$ catalyzed the tritium labeling of methyl 6-methoxynaphth-2-ylacetate at C1 and C3.

Keywords: Iridium; Deuteration; Tritiation; Isotope exchange; Metallacycle

1. Introduction

We have previously described the deuterium exchange labeling of a variety of chemical structures catalyzed by the complex $[IrH_2(acetone)_2(PPh_3)_2]BF_4$ (1) [1,2] and have since applied the general method with tritium in a number of cases [3,4]. Recently, Hesk et al. [5] have reported the deuteration of acetanilides and other substituted aromatics using $[Ir(cod)(PCy_3)(py)]PF_6$ ('Crabtree's Catalyst'). The former complex was found to catalyze exchange only of hydrogens exactly four bonds away from a coordinative heteroatom in the substrate. This is thought to reflect a strong preference of the metal center for formation of a five-membered metallacycle intermediate (e.g. A) upon oxidative insertion into the activated C–H bond [6]. In contrast, the ability of Crabtree's Catalyst to label the ortho-positions of acetanilides indicates relatively facile six-membered ring formation (e.g. B) by the catalytic species derived from this complex.



A B

The report of Hesk et al. prompts us to describe some of our work with complexes of the type $[Ir(cod)L_2]X$ (L = phosphine ligand, X = BF_4 or PF_6), which provides additional information about the effects of ligands on the regioselectivity of hydrogen isotope exchange by this metal center. This information can aid in the selection of catalysts best suited for labeling of particular substrates of interest.

2. Results

We began exploring the use of 1,5-cyclooctadiene complexes as pre-catalysts, rather than pre-reduced

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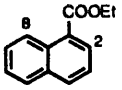
PII S0022-328X(96)06413-3

Table 1
Deuteration of ethyl 1-naphthoate



Complex (no. of trials)	Loading (mol%)	(Mol D) mol^{-1} at C2	(Mol D) mol^{-1} at C8
(2) $[Ir(cod)(PPh_3)_2]BF_4$ ($n = 23$)	2.2	0.90	— [a]
$[Ir(cod)[P(m\text{-}MePh)_3]_2]PF_6$ ($n = 2$)	2.0	0.88	— [a]
(4) $[Ir(cod)(PMePh_2)_2]PF_6$ ($n = 2$)	2.5	0.72	— [a]
$[Ir(cod)[P(p\text{-}MeOPh)_3]_2]PF_6$	1.8	0.87	— [a]
(3) $[Ir(cod)(dppe)]BF_4$			
($n = 6$)	2.5	0.54	0.35
($n = 6$)	5	0.54	0.33
($n = 7$)	13	0.79	0.54
$[Ir(cod)(dppb)]BF_4$	19	0.83	0.15
Crabtree's Catalyst	2.5	0.22	—a
	8	0.23	— [a]
	25	0.38	— [a]
	50	0.55	— [a]

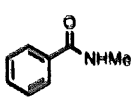
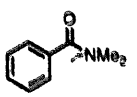
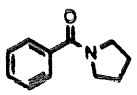
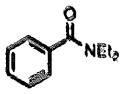
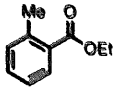
[a] Less than 0.05 mol D/mol at site.

complexes such as **1**, because it was more convenient to obtain a wide variety of complexes in this series (they are either commercially available or prepared in one synthetic step), and because control experiments with some model substrates showed that exchange labeling was slightly more efficient starting with $[Ir(cod)(PPh_3)_2]BF_4$ (**2**) compared with **1** [7].

Our results show that the complex $[Ir(cod)(dppe)]BF_4$ (**3**), which contains the bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe), equally catalyzes the exchange of hydrogens four and five bonds away from a coordinating heteroatom, whereas a variety of analogous $[Ir(cod)L_2]X$ complexes containing monodentate phosphines are selective only for hydrogens four bonds away. Only when the amount of the latter complex vs. substrate becomes large (e.g. 50 mol% or more) can significant five-bond exchange sometimes be observed. Thus, control of exchange selectivity is possible both by choice of catalyst type and catalyst loading. This variation of selectivity is illustrated below in several substrate–complex combinations.

Stirred in methylene chloride solution in the presence of excess deuterium gas at 1 atm for 16–18 h, ethyl 1-naphthoate undergoes deuterium labeling exclusively at C2 when catalytic amounts of any of the monodentate complexes $[Ir(cod)L_2]X$ ($L = PPh_3$, $P(m\text{-}MePh)_3$, $P(p\text{-}MePh)_3$, $P(p\text{-}MeOPh)_3$ and $PMePh_2$; $X = BF_4$ or PF_6) are used, as shown in Table 1. The amount and location of deuterium in purified substrates was assessed by ^1H NMR (CD_3OD: δ 8.10 for C2-H and δ 8.82 for C8-H), and the results were confirmed in selected cases by additional ^2H NMR analysis. The extent of labeling at C2 under these conditions is uniformly high, with little variation due to the structure of the phosphine ligand. (The issue of ligand influence in exchange catalysis in this series has been examined in

Table 2
Deuteration of benzoyl compounds

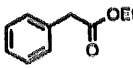
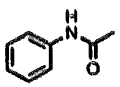
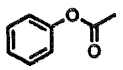
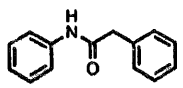
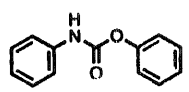
Substrate	Complex	Loading (mol%)	(Mol D) mol^{-1} (MS)	Location (NMR)
	**2**	1.5	1.7	*ortho*:NMe 19:1
	3	1.7	1.55	26:1
	**2**	1.6	0.17	*ortho*:NMe 1:1
	2	28	1.98	0.7:1
	3	1.9	1.33	46:1
	**?**	1.9	1.11	*ortho* only
	3	2.2	1.44	*ortho* only
	**2**	1.9	0.06	*ortho* only
	2	28	1.02	*ortho* only
	3	2.2	1.33	*ortho* only
	**2**	1.6	0.67	C6 only
	3	1.9	0.14	C6 only
	3	43	0.76	C6 only

more detail in the case of benzophenone substrates [4].) In contrast to this, [Ir(cod)(dppe)]X (X = BF_4 or PF_6), catalyzes labeling at C8 as well, to only a slightly lesser degree compared with C2. On average, the labeling at C2 is less than with the monodentate complexes at the same catalyst loading, but owing to the additional labeling at C8 the overall deuterium content of the products is similar to that of the monodentate complexes; deuterium incorporation increased with greater catalyst loadings. The complex [Ir(cod)(dppb)]BF_4 (dppb = 1,2-bis(diphenylphosphino)butane) was less active than the dppe complex, and labeled C8 only to a small extent. Crabtree's Catalyst was less active yet, and did not label C8 (^{2}H NMR).

Comparisons of the activities of catalyst precursors **2** and **3** were carried out on a series of related benzamides; the data are displayed in Table 2. These are substrates which test the ability of catalysts to perform via five-membered metallacycle intermediates. In most cases, the labeling was highly selective for the ortho-positions in the ring. However, dimethylbenzamide was labeled by the PPh_3-containing complex **2** in the *N*-methyl groups to a degree as great as (or, at high catalyst loading, greater than) the phenyl ring, but this was not observed with the dppe complex **3**, which was more selective for aryl-H exchange. Significant alkyl labeling has previously been observed in a series of substituted *N,N*-dimethylbenzamides at low catalyst loadings of the pre-reduced PPh_3 complex **1** [1], and in other cases at higher loadings using tritium gas [4]. Analysis by ^{2}H NMR did show small amounts (5% or less of total) of deuterium to be incorporated into the methyl group of *N*-methylbenzamide by both **2** and **3**. The level of ortho-labeling by the two complexes was comparable and generally high. During these experiments, we observed that the catalytic activity of **2** was very sensitive to the purity of some of the substrates [2], but that of **3** was more rugged. Labeling of methyl 2-methylbenzoate in all cases was restricted to C6, with no observable label in the 2-methyl group.

Table 3 shows the results of experiments with substrates requiring six-membered metallacycle intermediates for hydrogen exchange. These results generally show that the bidentate complex is more effective at labeling this type of substrate. Of the first three substrates listed, only acetanilide is labeled by the monodentate complexes **2** and **4**, and higher loadings are required for significant labeling; the other two substrates are not labeled by the monodentate complexes even when used at stoichiometric levels. In comparison,

Table 3
Deuteration of benzacyl analogs

Substrate	Complex	Loading (mol%)	Mol D/mol (MS)	Location (NMR)
	2	1.8	< 0.02	ND
	2	100	< 0.02	ND
	3	2.1	0.05	*ortho*
	3	5.0	0.13	*ortho*
	2	1.5	0.22	*ortho*
	2	100	0.79	*ortho*
	3	1.7	1.54	*ortho*
	4	100	1.71	*ortho*
	2	35	< .0.02	ND
	3	38	1.37	*ortho*
				N-ring:C-ring *ortho* positions:
	2	4.6	0.10	> 20:1
	2	50	1.66	"
	3	5.4	3.35	0.9:1
	4	5.4	1.09	> 20:1
	4	50	2.30	2.3:1
	Crabtree's	5.2	1.55	10:1
	Crabtree's	50	2.85	1:1
				N-ring:O-ring *ortho* positions:
	2	100	0.69	> 20:1
	3	50	1.95	2.6:1
	3	100	2.90	1.5:1
	3	200	3.44	1:1

ND = not determined.

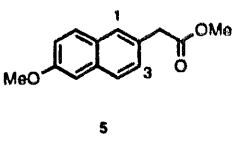
Table 4
Labeling of methyl 6-methoxynaphth-2-yl acetate

Complex	Loading (mol%)	(Mol D) mol^{-1} (MS)	Ratio of label (C3:C1)
4	100	< 0.02	ND
4	200	< 0.02	ND
3	50	0.22	> 6.1
3	110	0.53	~ 11:1
3	230	1.07	2.2:1
3 (tritiation)	150	0.24 (7 Ci $mmol^{-1}$)	4.7:1

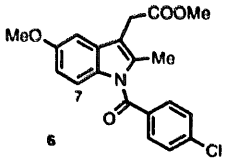
ND = not determined.

the bidentate complex **3** catalyzes exchange of all these substrates relatively more efficiently. The last two compounds, *N*-phenyl phenylacetamide and *N,O*-diphenylcarbamate, can be labeled in either ring, and therefore provide information not only about degree of labeling but also, by measurement of the degree of labeling of the two rings within the same compound, indicate the catalysts' abilities to mediate exchange ostensibly via six-membered metallacycles of different types. Overall, deuterium incorporation into *N*-phenyl phenylacetamide increases as **2** < **4** < Crabtree's < **3**, with the bidentate complex being most active. The selectivity of labeling the N-ring compared with the C-ring decreased in the same order, i.e. **2** > **4** > Crabtree's > **3**, with the PPh_3 complex **2** being completely selective for the N-ring even at high loadings, and the dppe complex **3** being able to label both rings equally even at low catalyst loading. Similar trends are apparent with *N,O*-diphenylcarbamate, with the N-ring being more easily labeled than the O-ring. It is interesting to note the increased activity of the $PMePh_2$ complex (**4**) over that of the PPh_3 complex (**2**), which could be ascribed either to the increased electron density on the iridium center, or the less sterically congested environment around the metal.

Methyl 6-methoxynaphth-2-yl acetate (**5**), derived from metabolism of the anti-inflammatory drug nabumetone [8], was needed in tritiated form at relatively low specific activity for pharmacokinetic experiments. As shown in Table 4, compound **5** is not labeled by the monodentate complex $[Ir(cod)(PMePh_2)_2]PF_6$ (**4**), even when used at superstoichiometric amounts. Compound **5** is, however, labeled both at C1 and C3 by $[Ir(cod)(dppe)]BF_4$ (**3**). Rather high loadings are required to achieve reasonable levels of deuterium incorporation; note that **5** is an analog of ethyl phenylacetate (Table 3), which is also not a particularly good substrate. Deuterium incorporation at C3 is favored over that at C1, probably because of steric interactions with phosphine ligands in the metallacycle intermediate. Nevertheless, the deuterium experiments suggested that the activity of the bidentate complex was sufficient to induce labeling, and this one was used in a tritium exchange reaction on **5**. Since high specific activity was not required, we used tritium gas recovered from previous tritiations; this tritium is diluted with an undetermined amount of hydrogen. Thus, stirring of a methylene chloride solution of **5** (22 μmol) and complex **3** (33 μmol) under 165 μmol of recovered tritium gas at room temperature for 24 h provided, after purification by HPLC, 36 mCi of [^{3}H]**5** at 98% radiochemical purity and 7 Ci $mmol^{-1}$ specific activity, more than sufficient for the intended studies. Tritium NMR analysis showed that tritium was located only at C1 and C3, in the ratio 1:4.7, in line with the results of the deuterium experiments.



5



6

Finally, a more complex example typical of many pharmaceutical compounds, indomethacin methyl ester (**6**), was exposed to stirring in solution under deuterium gas in the presence of various complexes (Table 5). Compound **6** possesses a carbonyl group which can be viewed as either part of a benzamide moiety (capable of being labeled in the phenyl ring ortho to the carbonyl via a five-membered metallacycle) or an acylindole (capable of being labeled at the indole C7 position via a six-membered metallacycle). Thus, this compound is a good test both of the effect of extraneous functionality and the relative regioselectivity of different catalysts.

Interestingly, all catalysts labeled both sites in compound **6** to some degree. The data on $[Ir(cod)(PMePh_2)_2]PF_6$ (**4**) show moderate catalytic activity, generally increasing with loading. There is an approximate 2:1 preference (observable in data from

Table 5
Deuteration of indomethacin methyl ester

Complex	Loading (mol%)	(Mol D) mol^{-1} (MS)	Ratio of label in phenyl:indole rings
4	6	0.04	ND
4	10	0.07	phenyl
4	24	0.16	> 4:1
4	53	0.84	3.1:1
4	108	1.51	2.8:1
3	5	0.70	2.0:1
3	10	1.18	2.0:1
3	25	2.03	2.0:1
3	50	2.29	2.1:1
3	100	2.08	2.0:1
3	200	2.50	2.0:1
2	50	2.41	2.2:1
Crabtree's	4.6	0.05	ND
Crabtree's	87	0.31	~ 2:1

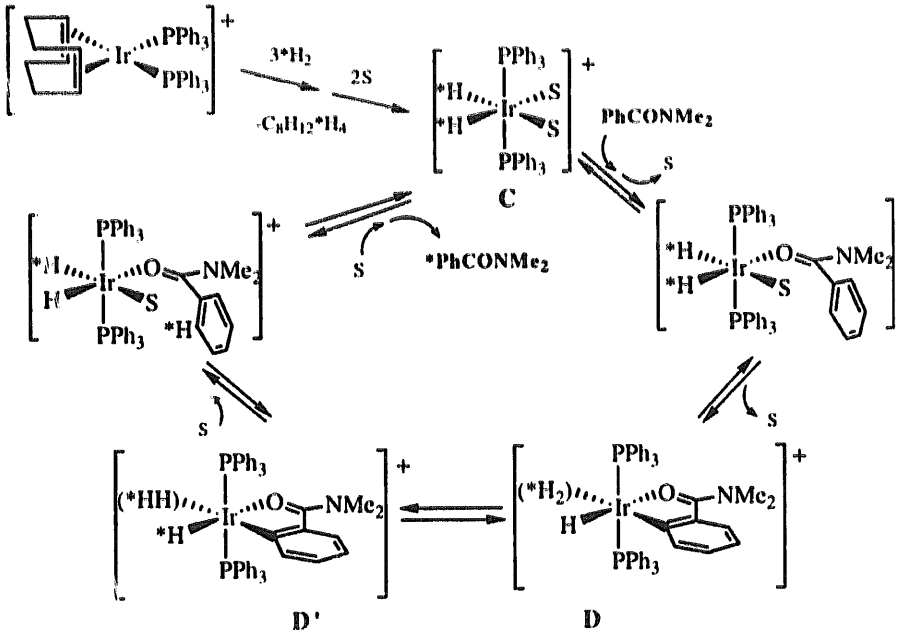
ND = not determined.

lower loading experiments; corrected for the number of exchangeable hydrogens) for deuterium exchange into the benzene ring ortho-positions compared with the indole benzo ring site. In contrast to these results, $[Ir(cod)(dppe)]BF_4$ (3) catalyzes exchange into both sites at the same rate, as indicated by the 1:1 ratio of incorporation (based on available hydrogens) into the two sites at all catalyst loadings. Exchange levels with 50 mol% of $[Ir(cod)(PPh_3)_2]BF_4$ (2) are quite high in both positions, obliterating any indication of relative exchange rates at the two sites. Crabtree's Catalyst was significantly less active than the other complexes in labeling compound 6.

3. Discussion and conclusions

The results summarized here show how the regioselectivity of catalytic exchange labeling, as well as the efficiency or rate, varies with the structure of the metal complex and the loading. The reaction time (16–18 h) was chosen to allow observation of a wide range of isotope incorporation levels, depending on substrate and catalyst loading, and served to allow rough comparison of labeling efficiency from case to case. Given the finite volume of deuterium gas available for exchange (see Section 4), the upper limit of deuteration at any exchangeable site was 80–90%, depending on reaction variables, since protium liberated from substrate exchangeable sites (and possibly adventitious water) would dilute the deuterium atmosphere. No time course experiments were performed in this study; however, such experiments were performed previously [2] with para-substituted ethyl benzoates under similar conditions; the catalyst was found to remain fully active for at least 4 days, and maximal deuterium levels in the substrates reached 0.85–0.90 mol D/exchangeable site. Therefore, the expectation is that deuterium levels in the current substrates not already maximally exchanged would increase with longer reaction times.

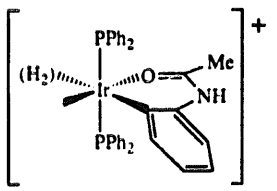
Eq. (1) depicts a hypothetical catalytic cycle for the case of the bis(triphenylphosphine) complex and dimethylbenzamide substrate. Ligand 'S' could be a loosely bound ligand (such as solvent, dihydrogen, adventitious water [6] or a second substrate molecule), or agostic bond, depending on the intermediate and the reaction conditions. The mutually trans disposition of the phosphine ligands is assumed by analogy with similar known structures [6,9] of iridium. The key to the exchange process is the fluxionality of the intermediate cyclic dihydrogen hydride (D ↔ D'), a well-known phenomenon in transition metal polyhydrides [10]. In this case it allows atmospheric (isotopic) hydrogen to move into the position cis to the Ir–C bond which is broken in the reverse of the cyclometallation, resulting in incorporation of the isotope into the ortho position of the substrate aryl ring.



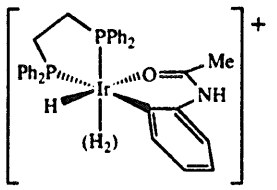
(1)

Our observation that the bis(triphenylphosphine) complexes usually label compounds only at positions consistent with five-membered metallacycle intermediates, whereas the bis(methyldiphenylphosphine) complex and Crabtree's Catalyst are capable of labeling in positions consistent with six-membered metallacycles, may be the result of differences in steric congestion around the metal center. Complexes with the less steri-

cally demanding ligands may more easily accommodate the larger and less planar six-member metallacycle rings than those with smaller ancillary ligands. In contrast to the complexes with monodentate ligands (e.g. the hypothetical cyclometal intermediate **E**), the dppe complex's phosphine ligands are mutually cis (as in **F**), which would significantly open up the coordination sphere in the region of the ligated substrate ring. In addition, the Ir–C bond in **F** may also be less labile than that in **E** because of the lesser trans effect of the *trans*-phosphine ligand in the former compared with the *trans*-hydrogen in the latter.



E (Unfavorable)



F (Favorable)

With the growing body of information on the catalytic activities of an array of iridium complexes for hydrogen isotope exchange, it becomes increasingly possible to select a catalyst most suited to the particular substrate and labeling goals at hand. Various aspects of this chemistry are under continuing investigation in our laboratories.

4. Experimental

Complex **4** and $[Ir(cod)Cl]_2$ were obtained from Johnson Matthey, while Crabtree's Catalyst and other chemicals were from Aldrich Chemical Co. Dichloromethane in the exchange reactions was obtained from J.T. Baker, HPLC grade, and was used without prior purification. Complex **2**, its analogs with various substituents at the triphenylphosphine moiety, and $[Ir(cod)(dppb)]BF_4$ were prepared from the $[Ir(cod)Cl]_2$ dimer by direct treatment with the corresponding phosphine ligands according to the procedure of Haines et al. [11]. Complex $[Ir(cod)(dppe)]BF_4$ (**3**) was synthesized via $[Ir(cod)(EtOH)_2]BF_4$ intermediate from treatment of $[Ir(cod)Cl]_2$ dimer with $AgBF_4$ in ethanol [12], and recrystallized from ethanol. Methyl esters **5** and **6** were prepared from diazomethane derivatization of the corresponding acids, and purified by silica gel flash column chromatography. Various benzamides were made from amidation of benzyl chloride with the respective amines, followed by either vacuum distillation or flash column chromatographic purification. *N*-Phenyl phenylacetate and *N,O*-diphenylcarbamate were prepared similarly from phenylacetyl chloride and phenyl chloroformate with aniline. ^1H NMR spectra were recorded on Bruker AM400 or AM300 instruments in suitable deuterated solvents that could resolve signals of interest. ^2H NMR were recorded on a Bruker AM400 instrument. MS spectra were run by Oneida Research Services, Inc., Whitesboro, NY, in chemical ionization mode using methane as the reagent gas.

A typical exchange reaction involved dissolving 100 mg of a substrate and the appropriate amount of an Ir complex in 5 ml of CH_2Cl_2. Four such reaction flasks were then attached via a four-way adapter to the vacuum line, followed by freezing in liquid nitrogen, evacuation, and exposure to deuterium gas. Atmospheric pressure was reached by releasing excess pressure through a Firestone valve. The configuration of the glassware set-up allowed free access of substrates to 5–10 equivalents of deuterium gas, depending upon the molecular weights of the substrates and catalysts. Stirring at room temperature lasted for 16–18 h. Workup included evaporation of CH_2Cl_2, precipitation of the Ir complex residues in ether, and filtration through a plug of Celite packed in a disposable pipette. Removal of ether in the filtrate fractions directly afforded the products.

4.1. Tritiation of 5

A 5 mg (22 μmol) portion of ester **5** and 25.3 mg (33 μmol) of $[Ir(cod)(dppe)]BF_4$ in 1 ml of CH_2Cl_2 was exposed to 9.64 Ci (165 μmol) of recycled tritium gas (tritium–hydrogen mixture) at room temperature for 24 h. Removal of excess tritium gas and volatile materials afforded 76 mCi of crude [^{3}H]**5** with radiochemical purity of 90% by radio-TLC. Hydrolysis of the crude [^{3}H]**5** was achieved by stirring with 1 ml of 1 N aqueous NaOH in 2 ml of MeOH at room temperature for 1 h. Removal of solvents and preparative reverse-phase HPLC purification provided 36 mCi of the tritiated acid with 98% radiochemical purity by radio-HPLC (Zorbax SB-phenyl column (5 μm, 4.6 mm ID × 25 cm), 80/20 (v/v) 0.1 M NH_4OAc–MeCN, flow rate at 1.0 ml min^{-1}, UV detection at 227 nm and Ramona Radioactivity Detector, R_t = 11.1 min).

4.2. Spectroscopic data on compounds

4.2.1. N-Phenyl phenylacetamide

^1H NMR (CD_3OD): 3.65 (2H, s, Ar–CH_2–), 7.06 (1H, t, J = 9.8 Hz), 7.20–7.36 (7H, m), 7.53 (2H, dd, J = 11.3 and 1.4 Hz, N-*ortho*-Ar-*H*); MS, *m/z* (%): 423 (6), 252 (7), 240 (30), 212 (100, $(M + H)^+$).

4.2.2. N,O-Diphenylcarbamate

^1H NMR (CD_3OD): 7.05 (1H, t, J = 10.5 Hz, N-*para*-Ar-*H*), 7.17 (2H, d, J = 10.8 Hz, O-*ortho*-Ar-*H*), 7.23 (1H, t, J = 10.0 Hz, O-*para*-Ar-*H*), 7.29 (2H, t, J = 10.0 Hz, N-*meta*-Ar-*H*), 7.39 (2H, t, J = 10.7 Hz, O-*meta*-Ar-*H*), 7.48 (2H, d, J = 10.4 Hz,

N–*ortho*-Ar–*H*); MS, *m/z* (%): 242 (4), 214 (38, $(M+H)^+$), 120 (55), 95 (100).

4.2.3. Methyl 6-methoxynaphth-2-yl acetate (5)

^{1}H NMR (CD_3OD): 3.68 (3H, s, O–*Me*), 3.75 (2H, s, Ar–CH_2–), 3.88 (3H, s, CO_2*Me*), 7.10 (1H, dd, $J = 12.0$ and 3.3 Hz, 4-*H*), 7.19 (1H, d, $J = 3.3$ Hz, 5-*H*), 7.33 (1H, dd, J = 11.3 and 2.3 Hz, 3-*H*), 7.63 (1H, br s, 1-*H*), 7.68 (1H, d, $J = 11.6$ Hz, 7 or 8-*H*), 7.70 (1H, d, $J = 11.0$ Hz, 8 or 7-*H*); MS, *m/z* (%): 259 (7), 231 (63, $(M+H)^+$), 199 (25), 171 (100).

4.2.4. Indomethacin methyl ester (6)

^{1}H NMR ($CDCl_3$): 2.39 (3H, s, Ar–*Me*), 3.67 (2H, s, Ar–CH_2–), 3.71 (3H, s, O–*Me*), 3.84 (3H, s, CO_2*Me*), 6.67 (1H, dd, $J = 12.0$ and 3.3 Hz, indole-6-*H*), 6.86 (1H, d, $J = 12.0$ Hz, indole-7-*H*), 6.96 (1H, d, $J = 3.3$ Hz, indole-4-*H*), 7.47 (2H, d, $J = 11.4$ Hz, *para*-Ar–*H*), 7.67 (2H, d, $J = 11.4$ Hz, *ortho*-Ar–*H*); MS, *m/z* (%): 412 (3), 400 (20), 372 (100, $(M+H)^+$), 312 (7), 139 (15).

Acknowledgements

We would like to thank Mr. Sidney H. Levinson for ^{3}H NMR measurements on [^{3}H]5, and D. Staiger for ^{2}H NMR measurements.

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