

Regioselective Benzylation of an Indazolyl-substituted Pyrazole under the Influence of Inorganic Solid Supported Bases†

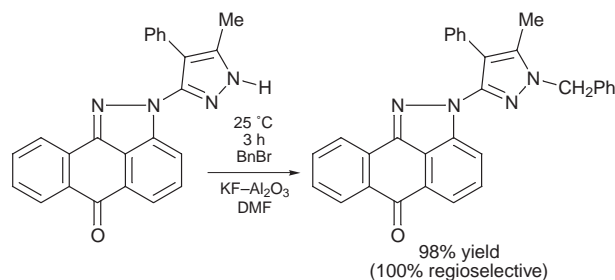
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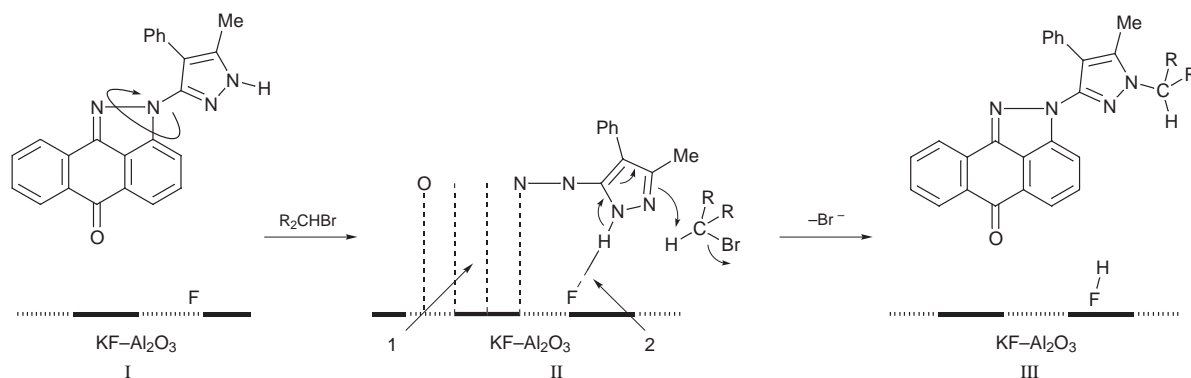
The benzylation of an indazolyl-substituted pyrazole under the influence of KOH–Al₂O₃, KF–Al₂O₃ and CsF–Al₂O₃ is investigated.

Many alkylation reactions on pyrazole¹ have been investigated and described as not being selective. Only in a few cases has regioselectivity has been described for special pyrazole derivatives and special reaction conditions, *e.g.* if diazomethane¹ or phase-transfer catalysts² are used. An alkylation of pyrazoles under the influence of inorganic solid supported bases has not been described until now. But in the literature this method has been used for the alkylation of imidazole³ and benzotriazole.⁴ In the case of benzotriazole a regioselectivity that depends on the choice of the solvent has been described.⁴ In a recently published work⁵ this method was used for the alkylation of a naphthoindazolyl pyrazole and has shown a 100% regioselectivity (Scheme 1).



Scheme 1 Selective benzylation of a pyrazole derivative⁵

The regioselectivity was explained by an adsorptive substrate mechanism. In this mechanism the aryl substituent adsorbs on the Al₂O₃-surface, while the pyrazole twists out of the plane of the aryl group and is fixed by a hydrogen

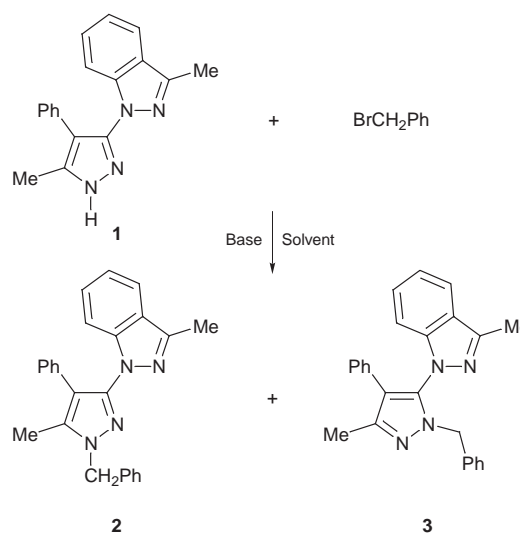


1: Adsorption of the aryl group on the Al₂O₃ surface, 2: hydrogen bond

Scheme 2 Alkylation mechanism under the influence of inorganic solid supported bases⁵

bond with the surface of the base (Scheme 2, II)⁵ With a shift of double bonds around the pyrazole ring, the alkylation takes place at the nitrogen neighbouring the methyl group (Scheme 2, III).⁵

Our interest was in whether the described reaction is still regioselective in the case of smaller aryl groups. Therefore, the benzylation of the analogous, indazolyl-substituted pyrazole **1** was investigated (Scheme 3).



Scheme 3

* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

The benzylation has been investigated under the influence of KOH–Al₂O₃, KF–Al₂O₃ and CsF–Al₂O₃. The ratio of the isomers **2** and **3** was determined *via* the intensities of the methylene peaks in the ¹H NMR spectra. To judge

Table 1 Benzylation of **1** under various reaction conditions

No.	Solvent	Amount/ml	Base	2 (%) ^a	3 (%) ^a
1	Acetone	10	KOH–Al ₂ O ₃	60	40
2	Ethyl acetate	30	KOH–Al ₂ O ₃	90	10
3	Acetonitrile	30	KOH–Al ₂ O ₃	Decomposition	
4	THF	10	KOH–Al ₂ O ₃	87	13
5	1,4-Dioxane	15	KOH–Al ₂ O ₃	91	9
6	DMF	10	KOH–Al ₂ O ₃	65	35
7	Acetone	10	KF–Al ₂ O ₃	70	30
8	Ethyl acetate	30	KF–Al ₂ O ₃	90	10
9	Acetonitrile	30	KF–Al ₂ O ₃	Decomposition	
10	THF	10	KF–Al ₂ O ₃	85	15
11	1,4-Dioxane	15	KF–Al ₂ O ₃	100	0
12	DMF	10	KF–Al ₂ O ₃	63	37
13	Acetone	10	CsF–Al ₂ O ₃	70	30
14	Ethyl acetate	30	CsF–Al ₂ O ₃	100	0
15	Acetonitrile	30	CsF–Al ₂ O ₃	Decomposition	
16	THF	10	CsF–Al ₂ O ₃	100	0
17	1,4-Dioxane	15	CsF–Al ₂ O ₃	100	0
18	DMF	10	CsF–Al ₂ O ₃	84	16
19	Acetone	10	K ₂ CO ₃	58	42
20	1,4-Dioxane	15	K ₂ CO ₃	62	38
21	1,4-Dioxane	15	KOH	70	30
22	1,4-Dioxane	15	Et ₃ N	60	40

^a The ratio of isomers **2** and **3** were determined according to the intensities of the methylene peaks (**2**: $\delta = 5.41$, **3**: $\delta = 5.11$) in the ¹H NMR spectra (CDCl₃).

the regioselectivity, the products have also been produced in the presence of bases without a support. By comparison, benzylation under the influence of inorganic solid supported bases appeared to be highly selective. The results are listed in Table 1.

As seen in Table 1, the use of acetone and acetonitrile is disadvantageous to the reaction. Acetonitrile is not useful because it leads to decomposition of the products. On the other hand, ethyl acetate, THF and 1,4-dioxane support the selectivity.

The activity of the inorganic solid supported bases decreases in the order CsF–Al₂O₃ > KF–Al₂O₃ > KOH–Al₂O₃. This is explainable by decreasing strength of the hydrogen bond between the pyrazole and the surface of the base.

Other than in usual alkylation reactions, the used solvents have not been purified. Only 1,4-dioxane was stored over sodium metal, to prevent the formation of peroxides. As in all cases, the overall yield was between 90 and 100%, and traces of water seem not to disturb the reaction.

Experimental

1-(5-Methyl-4-phenyl-1H-pyrazol-3-yl)-3-methylindazole (**1**).—15 ml conc. H₂SO₄ was cooled to –15 °C in a 50 ml flask. At this temperature a solution of 1 g (3.5 mmole) 3,6-dimethyl-3,7-diphenyl-3H-pyrazolo[5,1-c][1,2,4]triazole⁶ in 5 ml ethyl acetate was slowly added. This solution was stirred at –15 °C for 2.5 h. It was then poured on 300 ml of crushed ice and neutralized with K₂CO₃ to pH 5. The organic material was extracted with ethyl acetate. The solution was dried over MgSO₄ and the solvent removed until 20 ml remained. The product precipitated overnight as colourless needles. It was filtered off by suction, washed with light petroleum (bp 60–90 °C) and dried over P₄O₁₀. Yield: 0.6 g (60%); mp 203 °C, *R*_f SiO₂/Et₂O 0.54, *R*_f (SiO₂/CH₂Cl₂): 0.02; δ_{H} (CDCl₃) 1.96 (s, 3H, 3-CH₃), 2.55 (s, 3H, 1-C-5-CH₃), 6.98–7.24 (m, 8H, 5,6,7-H + 1-C-4-C-2,3,4,5,6-H), 7.61 (d, 1H, 4-H), 10.65 (s, 1H, N-H); δ_{C} (CDCl₃) 10.58, 11.55, 110.35, 113.29, 120.13, 120.48, 123.19, 126.13, 126.83, 128.11, 128.28, 131.81, 137.48, 141.06, 142.59, 144.75. (Found: C, 75.03; H, 5.47; N, 19.61. Required: C, 74.98; H, 5.59; N, 19.43%).

CsF–Al₂O₃,³ KF–Al₂O₃³ and KOH–Al₂O₃⁴ were produced according to the literature.

1-(1-Benzyl-5-methyl-4-phenyl-1H-pyrazol-3-yl)-3-methylindazole (**2**) and 1-(1-Benzyl-3-methyl-4-phenyl-1H-pyrazol-5-yl)-3-methylindazole (**3**). 0.1 g (0.35 mmol) of **1** was dissolved in a 50 ml flask in the amount of solvent listed in Table 1. Then a 12-fold excess of inorganic solid supported base (4.2 mmole; 0.81 g KOH–Al₂O₃, 1.1 g KF–Al₂O₃,

1.83 g CsF–Al₂O₃) was added. After 5 min of stirring at room temperature 0.1 ml (0.14 g, 0.8 mmole) of benzyl bromide were added with a syringe. The mixture was stirred at room temperature for 4 h. It was then filtered and the filter and base were washed with solvent. The solvent was removed from the filtrate. The oily residue was dissolved in 50 ml of ethyl acetate; 50 ml of water and 3 ml of triethylamine were added and the mixture was stirred vigorously for 1 h. The two layers separated. The organic layer was washed 3 times with water and then dried over MgSO₄. After removal of the solvent the product remained as a colourless solid residue. It was dried under the vacuum of the belt drive pump for 1 h and then investigated by ¹H NMR (CDCl₃) (see Table 1).

The two isomers **2** and **3** have been separated *via* column chromatography (SiO₂/CH₂Cl₂:Et₂O = 30:1) and identified by NOE.

2: mp 130 °C, *R*_f(SiO₂/CH₂Cl₂:Et₂O = 30:1): 0.52; δ_{H} (CDCl₃) 2.30 (s, 3H, 3-CH₃), 2.57 (s, 3H, 1-C-5-CH₃), 5.41 (s, 2H, 1-N-1-CH₂), 7.12–7.32 (m, 13H, 5,6,7-H + 1-C-4-C-2,3,4,5,6-H + 1-N-CH₂-C-2,3,4,5,6-H), 7.62 (d, 1H, 4-H); δ_{C} (CDCl₃) 10.15, 11.56, 53.23, 110.39, 114.97, 119.53, 120.10, 123.50, 126.11, 126.29, 126.54, 127.33, 127.78, 128.35, 128.66, 131.45, 136.01, 137.03, 140.74, 143.40, 144.24. (Found: C, 78.95; H, 5.68; N, 14.67. Required: C, 79.34; H, 5.86; N, 14.80%).

3: mp 133 °C, *R*_f(SiO₂/CH₂Cl₂:Et₂O = 30:1): 0.43; δ_{H} (CDCl₃) 2.44 (s, 3H, 3-CH₃), 2.62 (s, 3H, 1-C-5-CH₃), 5.11 (s, 2H, 1-N-1-CH₂), 6.70 (d, 1H, 7-H), 7.07–7.11 (m, 12H, 5,6-H + 1-C-4-C-2,3,4,5,6-H + 1-N-CH₂-C-2,3,4,5,6-H), 7.59 (d, 1H, 4-H); δ_{C} (CDCl₃) 11.57, 13.19, 52.45, 109.26, 116.71, 119.59, 120.55, 123.31, 126.06, 126.85, 127.14, 127.79, 131.07, 133.59, 135.72, 141.37, 145.15, 145.33. (Found: C, 79.27; H, 5.65; N, 14.44. Required: C, 79.34; H, 5.65; N, 14.44%).

To remove the toxicity from the KF–Al₂O₃ and the CsF–Al₂O₃, which remained in the filter, it was suspended in 200 ml of water and CaCl₂ was added. Thus it was transformed into insoluble CaF₂ and was no longer bioavailable.

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References

- 1 K. Schofield, M. R. Grimmet and B. R. T. Keene, *Heteroaromatic Nitrogen Compounds "The Azoles"* Cambridge University Press, London, New York, Melbourne, 1976, S. 73.
- 2 S. Vega, E. Arranz, J. A. Díaz, E. Morante and C. Pérez, *J. Heterocycl. Chem.*, 1996, **33**, 151.
- 3 L. Wang and X. H. Sun; *Huaxue Tongbao*, 1993, **3** 8.
- 4 Y. H. Zheng, F. N. Wang, G. H. Deng and G. M. Li, *Xiangtan Dexue Ziran Kexue Xuebao*, 1991, **13**, 75.
- 5 M. W. Branco, *Dissertation Universität Heidelberg*, 1997, G. Ege and M. W. Branco, in preparation.
- 6 G. Ege, K. Gilbert and R. Heck, *Chem. Ber.*, 1984, **117**, 1726.