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Synthesis of 2-arylmaleimides *via* the Heck reaction

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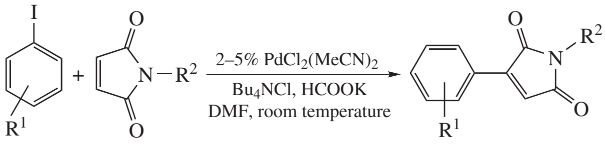
The Heck reaction of maleimides with aryl iodides in the presence of $PdCl_2(MeCN)_2$, Bu_4NCl and HCOOK affords the corresponding 2-arylmaleimides in moderate yields.

The most usual approach to 2-arylmaleimides is the Meervein arylation of maleimides with arene diazonium salts, with the yields ranging from low to moderate.[1–4] Palladium-catalyzed Heck arylation of maleimides is so far unknown, apparently due to their instability in basic media. Nonetheless, this reaction provides more and more new opportunities for the synthesis of olefinic compounds (a recent example is the synthesis of 2-arylmaleic anhydrides from fumaric acid[5]). Very broad variations in the nature of catalyst, base and additives are indeed possible.[6]



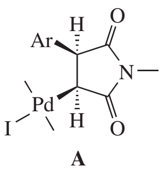
Scheme 1

In this work, we found that the $PdCl_2(MeCN)_2$–Bu_4NCl–HCOOK system in DMF at ambient temperature effects the Heck arylation of maleimides in moderate yields (Scheme 1). An initial study was made for the reaction of maleimide with 4-fluoroiodobenzene; the yields of 2-(4-fluorophenyl)maleimide under various conditions are given in Table 1.[†] Although this catalytic system was introduced to perform *reductive* arylation of norbornene,[7] in the case of maleimide, we observed only 2-arylmaleimide formation (Table 1). This implies that intermediate **A** undergoes elimination of H–PdI rather than substitution of palladium with formate hydrogen, in spite of *trans*-configuration of the H–C–C–PdI fragment (for mechanistic details of β-hydride elimination step, see ref. 6).

Table 1 Yield of 2-(4-fluorophenyl)maleimide from 4-fluoroiodobenzene and maleimide depending on reaction conditions.

Entry	HCOOK[a]	Bu_4NCl[a]	$PdCl_2(MeCN)_2$[a]	Time/days	Yield (%)[b]
1	2.5	1	0.02	8	34 (30)
2	KOAc, 2.5	1	0.02	1	—[c]
3	2.5	—	0.02	14	0
4	0.2	1.5	0.02	14	12[d]
5	0.1	1.5	0.02	3 at 60 °C	13[d]
6	2.5	1	0.05	3	35 (30)

[a]Moles per 1 mol of maleimide; ArI : maleimide = 1.25. [b]Estimated from the ^1H NMR spectrum of the crude product; yields of the isolated pure product are given in parentheses. [c]Extensive formation of deep red resinous matter. [d]Considerable amounts of unreacted ArI and maleimide by TLC.



A

If $NaHCO_3$ or KOAc was used instead of HCOOK (this system has been thoroughly studied[8–10]), maleimide deteriorated rapidly, probably, by anionic polymerization (entry 2). In the absence of Bu_4NCl, no arylation product was found (entry 3), in agreement with Jeffery's observations.[8] If excess Bu_4NCl was used with only a minimal amount of formate, the reaction had halted before all starting materials were consumed (entries 4

Table 2 Reactions of aryl iodides with maleimide and *N*-phenylmaleimide.

Entry	R^1	R^2	$PdCl_2(MeCN)_2$	Time/days	Isolated yield (%)[a]
1	4-F	Ph	0.02	5	40
2	4-F	H	0.05	3	30
3	4-OMe	Ph	0.02	6	30
4	4-OMe	H	0.02	12	42
5	4-Cl	Ph	0.02	3	32
6	$4-CO_2Me$	Ph	0.02	6	(28)[b]
7	$4-CO_2Me$	H	0.05	4	—[c]
8	$2-NO_2$	H	0.05	5	—

[a]Yield of pure 2-arylmaleimide with satisfactory mp and NMR purity of > 95%. [b]Estimated from the ^1H NMR spectrum of the crude product. [c]61% of unreacted ArI was recovered.

[†] *General procedure for the reactions of aryl iodides with* N*-phenylmaleimide and maleimide. A* mixture of ArI (5 mmol), *N*-phenylmaleimide (0.69 g, 4 mmol) or maleimide (0.39 g, 4 mmol), Bu_4NCl (1.11 g, 4 mmol), HCOOK (0.84 g, 10 mmol), $PdCl_2(MeCN)_2$ (0.021 g, 0.08 mmol or 0.052 g, 0.20 mmol) in DMF (4 ml) was stirred under argon at room temperature until the starting imide was consumed. Water (25 ml) was added and the mixture was extracted with EtOAc (40 + 20 ml). The extract was washed with water and evaporated *in vacuo*. The residue was extracted several times with hot hexane–benzene or toluene; on cooling the crude product precipitated, containing 5–10% Bu_4NI. It was recrystallized from small amounts of AcOH.

In reactions of maleimide, the reaction mixture instead of extraction with EtOAc was concentrated *in vacuo*, the residue was washed with water and further extracted as above.

*2-(4-Fluorophenyl)-*N*-phenylmaleimide* (Table 2, entry 1). Yellow crystals, mp 149.5–150.5 °C (from AcOH). ^1H NMR (500 MHz, $CDCl_3$) δ: 6.83 (s, 1H, =CH), 7.18 (pseudo-t, 2H, F–C–CH, $^3J_{HF} = {}^3J_{HH} = 8.6$ Hz), 7.38 (m, 3H, Ph), 7.49 (t, 2H, Ph, J 7.8 Hz), 8.02 (dd, 2H, F–C–CH=CH, $^3J_{HH}$ 8.9 Hz, $^4J_{HF}$ 7.1 Hz). MS, m/z (%): 267 (47, $M^{+\cdot}$), 238 (14, M – HCO), 211 (14, M – 2CO), 120 (100, M – 2CO – PhN), 91 (36, PhN^+). Found (%): C, 71.82; H, 3.81; N, 5.81. Calc. for $C_{16}H_{10}FNO_2$ (%): C, 71.91; H, 3.77; N, 5.24.

*2-(4-Methoxycarbonylphenyl)-*N*-phenylmaleimide* (Table 2, entry 6). ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.96 (s, 3H, COOMe), 6.99 (s, 1H, =CH), 7.40 (m, 3H, Ph), 7.50 (t, 2H, Ph, J 7.7 Hz), 8.06 (d, 2H, C_6H_4, J 8.4 Hz), 8.15 (d, 2H, C_6H_4, J 8.4 Hz). MS, m/z (%): 307 (25, $M^{+\cdot}$), 292 (8, M – OMe), 276 (5, M – HCO), 248 (55, M – COOMe), 129 (100).

and 5). Raising temperature or increasing the catalyst load allowed us to shorten the reaction time but not to improve the yield (entries 5 and 6).

The arylation was performed with other combinations of aryl iodide and maleimide, affording similar isolated yields of 30–40% (Table 2). *N*-Phenylmaleimide reacted notably faster than maleimide (*cf.* entry 1, Table 2 with entry 1, Table 1 or entry 3 with entry 4 in Table 2). Electron-withdrawing groups in aryl iodide make the reaction difficult: lower yield was observed with $R^1 = 4\text{-}CO_2Me$, $R^2 = Ph$ (entry 6), and no arylmaleimide was isolated with $R^1 = 4\text{-}CO_2Me$, $R^2 = H$ and $R^1 = 2\text{-}NO_2$ (entries 7, 8). Similar retarding effect was reported[10] for the Heck arylation of cinnamonitrile.

Thus, we discovered the first example of Heck arylation of maleimides. We are looking forward to increase yields of 2-arylmaleimides and also to employ them for the new syntheses of polycyclic compounds.

References

1 C. S. Rondestvedt, Jr. and O. Vogl, *J. Am. Chem. Soc.*, 1955, **77**, 2313.
2 C. S. Rondestvedt, Jr., M. J. Kalm and O. Vogl, *J. Am. Chem. Soc.*, 1956, **78**, 6115.
3 T. C. McKenzie, J. W. Epstein, W. J. Fanshawe, J. S. Dixon, A. C. Osterberg, L. P. Wennogle, B. A. Regan, M. S. Abel and L. R. Meyerson, *J. Med. Chem.*, 1984, **27**, 628.
4 A. Kar and N. P. Argade, *Synthesis*, 2005, 2284.
5 A. I. Roshchin, Yu. V. Kuznetsov and E. V. Polunin, *Izv. Akad. Nauk, Ser. Khim.*, 2007, **56**, 491 (*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 509).
6 I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009.
7 R. C. Larock and P. L. Johnson, *J. Chem. Soc., Chem. Commun.*, 1989, 1368.
8 T. Jeffery, *Tetrahedron*, 1996, **52**, 10113.
9 R. C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, **28**, 5291.
10 M. Moreno-Manas, R. Pleixats and A. Roglans, *Synlett*, 1997, 1157.

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