Insertion of arynes into carbon–halogen σ-bonds: regioselective acylation of aromatic rings†

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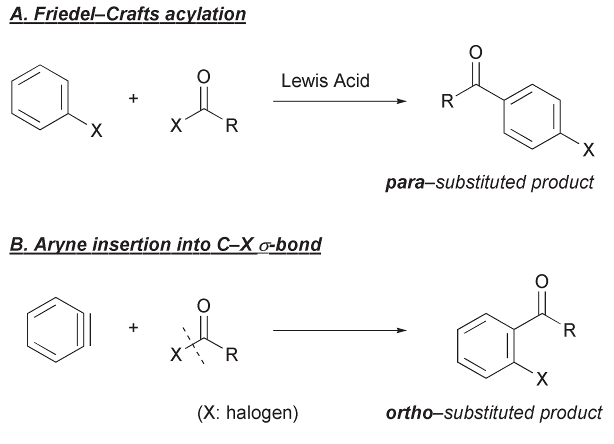
Arynes were found to insert into carbon–halogen σ-bonds of various acid halides, enabling acyl and halogen moieties to be introduced simultaneously into adjacent positions of aromatic rings.

Friedel–Crafts acylation reactions have been extensively studied and have been the most important method for the synthesis of aromatic ketones.[1] Owing to relatively large size of acyl moieties, the reactions of aromatic compounds bearing such *ortho-para*-directing groups as alkyl, alkoxy and halogen afford mainly or solely *para*-substituted products (Scheme 1, A). Hence, search for novel acylation reactions, in which acyl moieties are introduced regioselectively into an *ortho*-position of *ortho-para*-directing groups, has been a challenging and urgent subject in synthetic organic chemistry. In the course of our ongoing studies on insertion reactions of arynes into element–element σ-bonds,[2,3] which enable two functional groups to be introduced simultaneously into the contiguous positions of the aromatic rings, we have found that acid halides add across arynes at their carbonyl–halogen σ-bonds under extremely mild conditions. We report herein a new method for *ortho*-selective acylation of aromatic rings depending upon the aryne insertion into carbonyl–halogen σ-bonds, in which acyl and halogen moieties are incorporated into 1,2-positions of the aromatic rings all at once (Scheme 1, B).

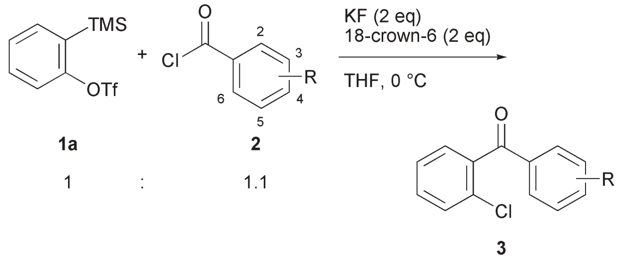


Scheme 1 Regioselectivities in acylation reactions.

We first carried out the reaction of benzyne with 3-methoxybenzoyl chloride (**2a**) in THF at 0 °C and observed that insertion into the carbonyl–chlorine σ-bond took place smoothly by simply mixing benzyne precursor **1a**,[4] **2a** and a fluoride ion (KF/18-crown-6), giving 2-chloro-3′-methoxybenzophenone (**3aa**) in 70% yield (Table 1, entry 1). Benzoyl chloride (**2b**) could also be applied to the reaction to afford a 68% yield of **3ab** (entry 2), and moreover, the reaction with substituted benzoyl chlorides possessing electron-neutral (**2c**), -withdrawing (**2d**) or -donating groups (**2e–2i**) produced the respective insertion products (**3ac–3ai**) in good to moderate yields (entries 3–9). Worthy to note is high functional group-compatibility of the reaction: treatment of bromo- (**2j**), cyano- (**2k**) or methoxycarbonyl-substituted benzoyl chloride (**2l**) with benzyne yielded the products (**3aj–3al**), leaving these functional groups intact (entries 10–12).

Besides benzoyl chloride derivatives, the reaction with other acid halides was also examined (Table 2). Thus, when 2-naphthoyl- (**2m**) or (*E*)-cinnamoyl chloride (**2n**) was allowed to react with benzyne, **3am** or **3an**[5] was formed in 50 or 58% yield (entries 1 and 2). Aliphatic acid chlorides (**2o–2s**) could participate in the reaction irrespective of the size of an alkyl group (entries 3–7), and a carbonyl–bromine σ-bond of benzoyl- (**2t**) or isobutyryl bromide

Table 1 Insertion of benzyne into substituted benzoyl chlorides[a]



Entry	R in **2**	Time/h	**3**	Yield[b] (%)
1	3-MeO (**2a**)	9	**3aa**	70
2	H (**2b**)	8.5	**3ab**	68
3	4-Ph (**2c**)	11.5	**3ac**	61
4	4-CF_3 (**2d**)	10	**3ad**	60
5	4-Me (**2e**)	9	**3ae**	55
6	2-Me (**2f**)	9	**3af**	52
7	2,5-Me_2 (**2g**)	9	**3ag**	52
8	2,4-Me_2 (**2h**)	8.5	**3ah**	43
9	4-MeO (**2i**)	9	**3ai**	42
10	4-Br (**2j**)	10	**3aj**	61
11[c]	4-CN (**2k**)	11	**3ak**	54
12	4-CO_2Me (**2l**)	11.5	**3al**	51

[a] The reaction was carried out in THF (2 mL) at 0 °C using **1a** (0.30 mmol), **2** (0.33 mmol), KF (0.60 mmol) and 18-crown-6 (0.60 mmol). [b] Isolated yield based on **1a**. [c] 4 eq. of KF.

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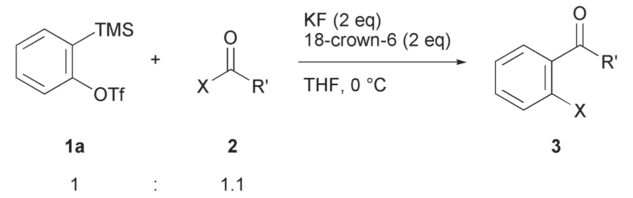
Table 2 Insertion of benzyne into various acid halides[a]



Entry	Acid halide	Time/h	3	Yield^b (%)
1	R′: 2-naphthyl, X: Cl (**2m**)	10	**3am**	50
2	R′: (*E*)-cinnamyl, X: Cl (**2n**)	9.5	**3an**	58
3	R′: *t*-Bu, X: Cl (**2o**)	10	**3ao**	57
4	R′: 1-adamantyl, X: Cl (**2p**)	22	**3ap**	48
5	R′: Cy, X: Cl (**2q**)	33.5	**3aq**	59
6	R′: *i*-Pr, X: Cl (**2r**)	23	**3ar**	46
7	R′: pentadecyl, X: Cl (**2s**)	90	**3as**	39
8	R′: Ph, X: Br (**2t**)	4.5	**3at**	54
9	R′: *i*-Pr, X: Br (**2u**)	6	**3au**	43
10	R′: PhO, X: Cl (**2v**)	8	**3av**	64
11	R′: EtO, X: Cl (**2w**)	11.5	**3aw**	56
12	R′: 9-carbazoyl, X: Cl (**2x**)	11	**3ax**	53

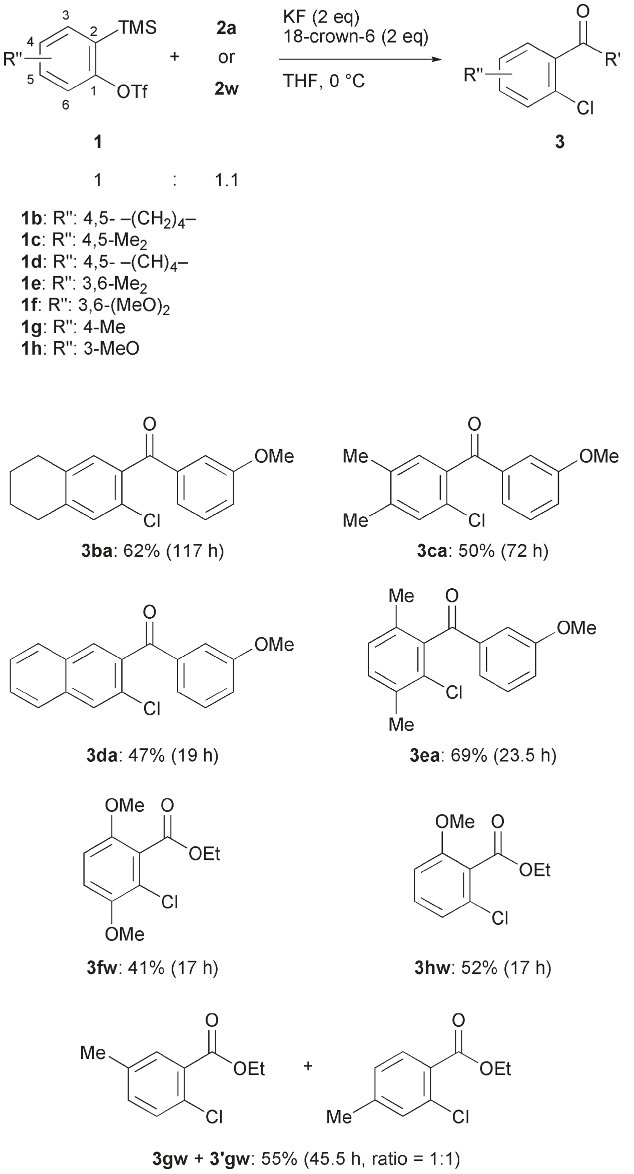
[a] The reaction was carried out in THF (2 mL) at 0 °C using **1a** (0.30 mmol), **2** (0.33 mmol), KF (0.60 mmol) and 18-crown-6 (0.60 mmol). [b] Isolated yield based on **1a**.

(**2u**) readily underwent the insertion of benzyne, enabling acyl and bromo moieties to be introduced into the adjacent positions as well (entries 8 and 9). Furthermore, a chloroformate (**2v** or **2w**) or a carbamoyl chloride (**2x**) was found to react with benzyne at their carbonyl–chlorine σ-bonds exclusively to provide **3av–3ax** in moderate yields, where the respective carbonyl–oxygen or carbonyl–nitrogen σ-bonds remained unchanged (entries 10–12).

The versatility of the present acylation can be further enhanced by employing variously substituted arynes. As depicted in Scheme 2, facile insertion of 4,5-dialkylated arynes (from **1b** or **1c**) or 2,3-naphthalyne (from **1d**) into **2a** was observed to give the corresponding polysubstituted diaryl ketones (**3ba–3da**). Despite the steric hindrance around the triple bond, the reaction of 3,6-dimethylbenzyne (from **1e**) or 3,6-dimethoxybenzyne (from **1f**) also proceeded, furnishing **3ea** or **3fw** in 69 or 41% yield. In addition, an unsymmetrical aryne, 4-methylbenzyne (from **1g**) efficiently reacted with **2w** to afford a mixture of two regioisomers (**3gw** : **3′gw** = 1 : 1),[6] whereas the reaction using 3-methoxybenzyne (from **1h**) produced solely **3hw** bearing the chloro moiety at the *meta* position to the methoxy moiety, which implies that a halogen atom in an acid halide acts as a nucleophilic site in the present reaction (*vide infra*).[7]

In view of salient electrophilicity of arynes[8] and the observed regioselectivity in the reaction of 3-methoxybenzyne, the insertion reaction would be initiated by a nucleophilic attack of a halogen atom in an acid halide (Scheme 3). The resulting zwitterion (**4**) then produces the insertion product by an intramolecular nucleophilic substitution at the carbonyl group.

In conclusion, we have disclosed the convenient acylation of aromatic rings *via* the novel insertion reaction of arynes into carbonyl–halogen σ-bonds, where the acyl moieties are incorporated into the *ortho*-positions to the halogen moieties with perfect regioselectivities. Based upon the present reaction, halogenated aryl ketones of structural diversity, whose regioselective synthesis by conventional Friedel–Crafts acylation would be difficult, can



1b: R'': 4,5- $-(CH_2)_4-$
1c: R'': 4,5-Me_2
1d: R'': 4,5- $-(CH)_4-$
1e: R'': 3,6-Me_2
1f: R'': 3,6-$(MeO)_2$
1g: R'': 4-Me
1h: R'': 3-MeO

3ba: 62% (117 h)

3ca: 50% (72 h)

3da: 47% (19 h)

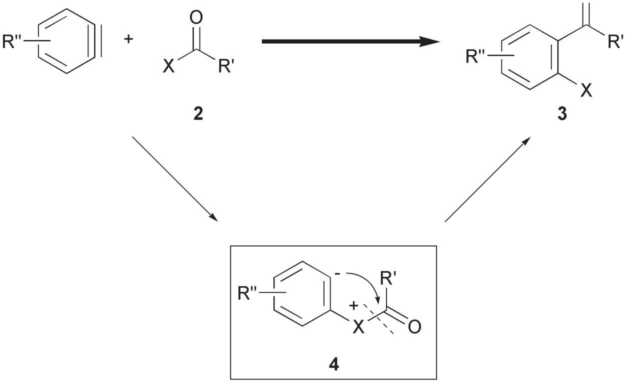
3ea: 69% (23.5 h)

3fw: 41% (17 h)

3hw: 52% (17 h)

3gw + 3'gw: 55% (45.5 h, ratio = 1:1)

Scheme 2 Insertion of substituted arynes.



Scheme 3 Reaction pathway for the insertion reaction.

readily be fabricated in a straightforward manner. Further studies on expansion of reaction scope are in progress.

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Notes and references

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5 (*E*)-Configuration of the cinnamyl group in **2n** is retained in **3an**.

6 This result confirms that the present reaction indeed proceeds through an aryne intermediate.

7 Owing to an electron-withdrawing inductive effect and a steric effect of the methoxy moiety, 3-methoxybenzyne generally accepts a nucleophilic attack at the *meta* position to the methoxy moiety.

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